"TO STUDY PALLIATION OF SYMPTOMS BY A HYPOFRACTIONATED RADIOTHERAPY SCHEDULE IN INOPERABLE SQUAMOUS CELL CANCERS OF THE ORAL CAVITY."

DEPARTMENT OF RADIOTHERAPY
CHRISTIAN MEDICAL COLLEGE
VELLORE 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF
MD BRANCH RADIOTHERAPY
EXAMINATION APRIL 2017

TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI - 600032.

CHRISTIAN MEDICAL COLLEGE, VELLORE

DEPARTMENT OF RADIOTHERAPY

Certificate

This is to certify that the dissertation **TO STUDY PALLIATION OF SYMPTOMS BY A HYPOFRACTIONATED RADIOTHERAPY SCHEDULE IN INOPERABLE SQUAMOUS CELL CANCERS OF THE ORAL CAVITY."** is a bonafide work done by Dr.Arun Krishnan.M.P, Post Graduate Student in the Department of Radiotherapy, Christian Medical College, Vellore during the period from April 2014 to April 2017 and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch Radiotherapy examination conducted in April 2017.

Guide

Dr. Simon P Pavamani

Professor

Department of Radiotherapy

Christian Medical College

Vellore, India – 632004

Certificate

This is to certify that the dissertation "**TO STUDY PALLIATION OF SYMPTOMS BY A HYPOFRACTIONATED RADIOTHERAPY SCHEDULE IN INOPERABLE SQUAMOUS CELL CANCERS OF THE ORAL CAVITY".** is a bonafide work done by Dr.Arun Krishnan.M.P, Post Graduate Student in the Department of Radiotherapy, Christian Medical College, Vellore during the period from April 2014 to April 2017 and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch Radiotherapy examination conducted in April 2017.

Principal

Christian Medical College
Vellore, India- 632004

Dr. Selvamani B
Prof and Head of the department
Department of Radiotherapy
Christian Medical College
Vellore, India - 632004

Certificate

This is to certify that the dissertation **"TO STUDY PALLIATION OF SYMPTOMS BY A HYPOFRACTIONATED RADIOTHERAPY SCHEDULE IN INOPERABLE SQUAMOUS CELL CANCERS OF THE ORAL CAVITY"**is a bonafide work done by Dr.Arun Krishnan.M.P, Post Graduate Student in the Department of Radiotherapy, Christian Medical College, Vellore during the period from April 2014 to April 2017 and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfilment of the MD Branch Radiotherapy examination conducted in April 2017.

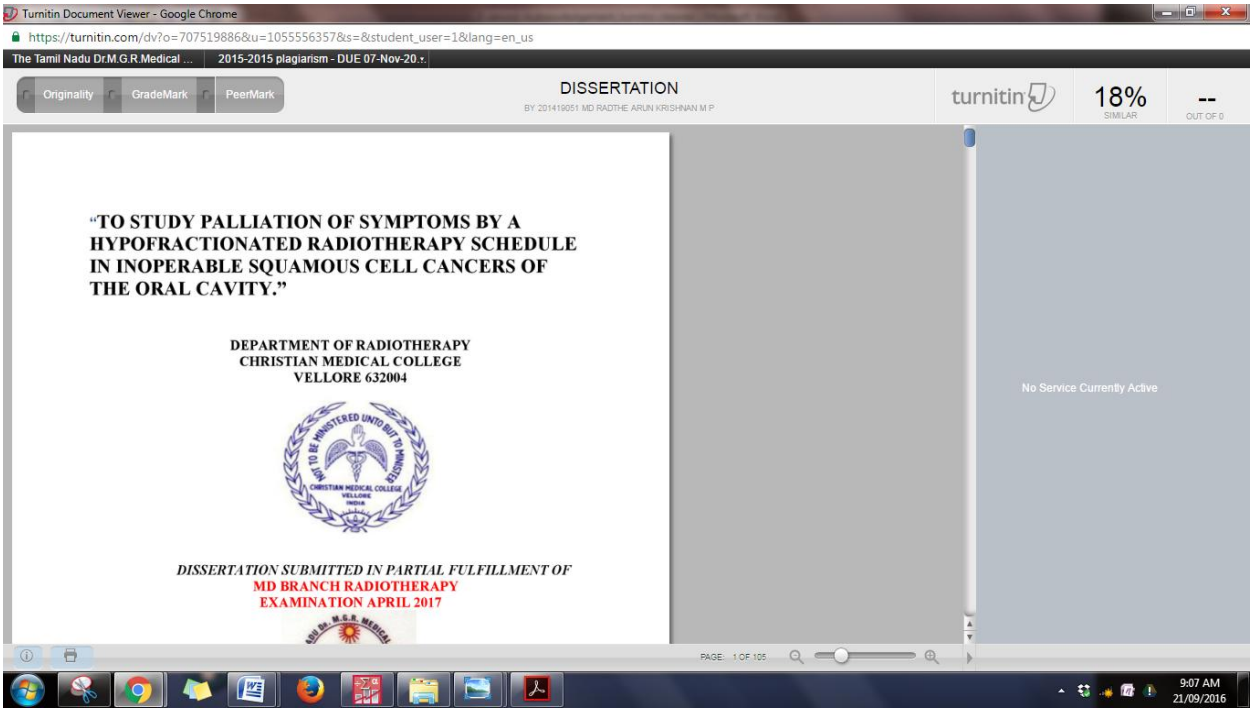
Dr .Arun Krishnan .M .P

PG REGISTRAR,

DEPARTMENT OF RADIOTHERAPY,

CHRISTIAN MEDICAL COLLEGE,

VELLORE


Turnitin Document Viewer - Google Chrome
https://turnitin.com/dv?o=707519886&u=1055556357&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical ...
2015-2015 plagiarism - DUE 07-Nov-20.
Originality
GradeMark
PeerMark
DISSERTATION
BY 201419051 MD RADTHE ARUN KRISHNAN M P
turnitin
18%
SIMILAR
--
OUT OF 0
"TO STUDY PALLIATION OF SYMPTOMS BY A HYPOFRACTIONATED RADIOTHERAPY SCHEDULE IN INOPERABLE SQUAMOUS CELL CANCERS OF THE ORAL CAVITY."
DEPARTMENT OF RADIOTHERAPY
CHRISTIAN MEDICAL COLLEGE
VELLORE 632004
DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF
MD BRANCH RADIOTHERAPY
EXAMINATION APRIL 2017
No Service Currently Active
PAGE: 1 OF 105
9:07 AM
21/09/2016

Turnitin Originality Report

DISSERTATION by 201419051 Md Radthe Arun Krishnan M P

From 2015-2015 plagiarism (The Tamil Nadu Dr.M.G.R.Medical Uty 2015-16 Examinations)

- Processed on 19-Sep-2016 20:38 IST
- ID: 707519886
- Word Count: 13384

Similarity Index
18%
Similarity by Source

Internet Sources:
16%
Publications:
13%
Student Papers:
6%

sources:

1 2% match (Internet from 06-Aug-2008)
http://www.stonybrookhospital.com/cancerregistry/TU2C046.pdf

2 1% match (Internet from 01-Aug-2013)
http://www.medicalphysicist.co.uk/Basic_Radiobiology.pdf

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

February 25, 2015

Dr. Arun Krishnan. M. P
PG Registrar
Department of Radiotherapy
Christian Medical College, Vellore 632 004

Sub: **Fluid Research Grant Project:**
To study palliation of symptoms by a hypo fractionated radiotherapy schedule in Inoperable Squamous Cell Cancers of the oral cavity.
Dr. Arun Krishnan. M. P, PG Registrar, Dr. Simon Pavamani, Dr. Jenifer Jeba .S, Radiotherapy, Dr. Pranay Gaikwad, Surgery, Mrs. Tunny Sebastian, Biostatistics, CMC, Vellore.

Ref: IRB Min No: 9257 [OBSERVE] dated 12.01.2015

Dear Dr. Arun Krishnan. M. P,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB Endo),FRACP(Endo),FRCP Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Simon Pavamani, Radiotherapy, CMC, Vellore.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

February 25, 2015

Dr. Arun Krishnan. M. P
PG Registrar
Department of Radiotherapy
Christian Medical College, Vellore 632 004

Sub: **Fluid Research Grant Project:**
To study palliation of symptoms by a hypo fractionated radiotherapy schedule in Inoperable Squamous Cell Cancers of the oral cavity.
Dr. Arun Krishnan. M. P, PG Registrar, Dr. Simon Pavamani, Dr. Jenifer Jeba .S, Radiotherapy, Dr. Pranay Gaikwad, Surgery, Mrs. Tunny Sebastian, Biostatistics, CMC, Vellore.

Ref: IRB Min No: 9257 [OBSERVE] dated 12.01.2015

Dear Dr. Arun Krishnan. M. P,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "To study palliation of symptoms by a hypo fractionated radiotherapy schedule in Inoperable Squamous Cell Cancers of the oral cavity." on January 12th 2015.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Arun Krishnan. M. P, Simon Pavamani, .Jenifer Jeba .S, Pranay Gaikwad, Mrs. Tunny Sebastian
3. Informed consent form (English, Tamil, Hindi, Malayalam & Bengali)
4. Information Sheet (English, Tamil, Hindi, Malayalam & Bengali)
5. Questionnaire (English, Tamil, Hindi, Malayalam & Bengali)
6. Proforma
7. No of documents 1 – 6

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on January 12th 2015 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing	Internal, Nurse
Mr. C. Sampath	BSc, BL	Legal Expert, Vellore	External, Legal Expert
Rev. Joseph Devaraj	B. Sc, BD	Chaplaincy Department, CMC	Internal, Social Scientist
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson, IRB; Member Secretary (Ethics Committee),IRB	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent.** On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 8,000/- INR (Rupees Eight Thousand only) will be granted for 2 years.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Simon Pavamani, Radiotherapy, CMC, Vellore.

IRB Min No: 9257 [OBSERVE] dated 12.01.2015

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Contents

Acknowledgement

I extend my gratitude to all those who contributed towards making this study possible. I am grateful to God Almighty and all those who have directly or indirectly helped me in this venture.

I thank my Guide, Prof. Dr. Simon P. Pavamani, Professor, Department of Radiotherapy for his meticulous guidance, constant support and motivation from initiation to the end of the dissertation, without whom the study would not have been possible.

I would like to express my sincere gratitude to my Co-Guide, Dr. Jenifer Jeba. S, Associate Professor, Palliative Care Unit, Department of Radiation Therapy for her immense patience and valuable suggestions.

I would like to thank my co-guide Dr. Pranay Gaikwad, (Professor, Department of Surgery) for his able guidance and timely advice which helped me through this journey.

I thank Prof. Dr. Selvamani B (Head of Department of Radiotherapy),Dr. Balukrishna S(Associate Professor Department of Radiotherapy), Dr. Thomas Samuel Ram (Professor Department of Radiotherapy), Dr. Sunitha Susan Varghese (Assistant Professor Department of Radiotherapy),Dr. Naveen Kumar M B(Assistant Professor Department of Radiotherapy) for their concern, care and encouragement.

I extend my sincere gratitude to Tunny Sebastian, who helped me patiently and made valiant efforts for the output and statistical analysis.

I would like to thank Dr. Thambu David who was available at all stages of this thesis and for timely advice at crucial points of this dissertation.

I am grateful to the entire Department of Radiotherapy, including faculty, colleagues, and technicians, for all the support rendered in preparing this dissertation.

I wish to thank all my patients for their co-operation in this study.

I would like to thank my parents and family members for their encouragement and support.

AIM

To study palliation of symptoms by a hypofractionated radiotherapy schedule in inoperable squamous cell cancers of the oral Cavity.

Objectives

Primary Objective: To assess and quantify symptom relief and duration of symptom relief in patients with inoperable squamous cell carcinoma of oral cavity undergoing hypofractionated radiotherapy using validated quality of life questionnaire.

Secondary Objective: To assess clinical tumour response in inoperable squamous cell carcinoma of oral cavity patients undergoing hypofractionated radiotherapy.

Introduction

Oral cavity malignancies present commonly in loco regionally advanced stages of the disease. The recommended primary modality of treatment is surgery. Patients with Stage IV B & IV C are generally considered inoperable. As the survival in this group of patients is low, the main intent of treatment is palliation. Chemotherapy and radiotherapy are the palliative options; however, chemotherapy alone has limited benefit in this group of patients.

It is widely recognized that Palliative Radiotherapy provides effective palliation and an improvement in 'Quality Of Life' (QOL) in advanced, incurable malignancies. Common symptoms in this group of patients include pain, dysphagia, odynophagia, trismus, cough and respiratory distress[).

This study observed the palliation of symptoms in patients with inoperable Oral Cavity Cancers who were treated by a standard palliative radiotherapy regime. These patients were treated with a standard palliative radiotherapy regimen of 50 Gy in 4 weeks (five fractions per week). Quality of life questionnaires were administered to assess the subjective symptoms and quality of life before treatment, after treatment and at the first follow up (4 to 6 weeks after the treatment). The Quality of life questionnaires used in this study were EORTC QLQ-C30 & EORTC QLQ - H&N35 & Euro Qol .The type of tumour response was documented clinically & with imaging, if indicated. The duration of the response was also studied.

Most studies on Palliative RT in Head & Neck Cancers have a heterogeneous mix of patients belonging to the various Head & Neck cancer sub sites. Majority of the studies were retrospective in nature. This makes it difficult to draw meaningful conclusions from the studies while treating patients in our clinics.

Hence we focussed on patients with Inoperable Oral Cavity Cancers who were prospectively recruited and treated with a specific palliative radiotherapy regime, with a systematic documentation of the symptom relief using validated quality of life questionnaires.

Epidemiology: Global, Indian and Regional scenario

Head and neck cancer ranks the sixth position among the common cancers worldwide(1) . Oral cavity cancers form a sub site of head and neck malignancies ranks the eleventh most common cancer worldwide. The annual estimated incidence of is around 300,000 for oral cavity malignancies globally(2). Incidence wise it forms 2.1% of all malignancies.

Estimated incidence, mortality and 5-year prevalence: both sexes

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	300373	2.1	4.0	145353	1.8	1.9	702149	2.2	13.5
Nasopharynx	86691	0.6	1.2	50831	0.6	0.7	228698	0.7	4.4
Other pharynx	142387	1.0	1.9	96105	1.2	1.3	309991	1.0	6.0
Oesophagus	455784	3.2	5.9	400169	4.9	5.0	464063	1.4	8.9
Stomach	951594	6.8	12.1	723073	8.8	8.9	1538127	4.7	29.6
Colorectum	1360602	9.7	17.2	693933	8.5	8.4	3543582	10.9	68.2
Liver	782451	5.6	10.1	745533	9.1	9.5	633170	2.0	12.2
Gallbladder	178101	1.3	2.2	142823	1.7	1.7	205646	0.6	4.0
Pancreas	337872	2.4	4.2	330391	4.0	4.1	211544	0.7	4.1
Larynx	156877	1.1	2.1	83376	1.0	1.1	441675	1.4	8.5
Lung	1824701	13.0	23.1	1589925	19.4	19.7	1893078	5.8	36.5
Melanoma of skin	232130	1.7	3.0	55488	0.7	0.7	869754	2.7	16.8

Fig 1: Incidence, Mortality and prevalence of oral cancer

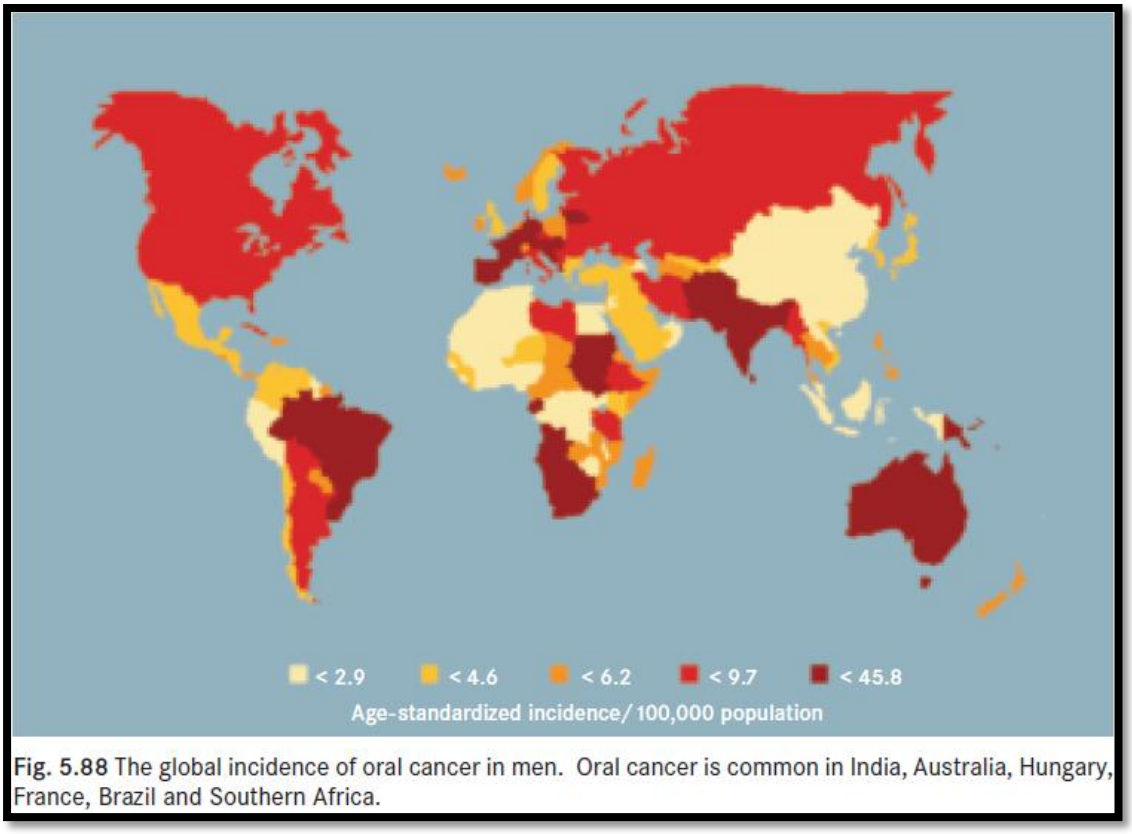


Fig. 5.88 The global incidence of oral cancer in men. Oral cancer is common in India, Australia, Hungary, France, Brazil and Southern Africa.

Fig 2: Global Incidence of oral cancer in men(3)

The prevalence of oral cavity cancer is very high in south and south East Asian countries and is showing an increasing trend in incidence. Various ethnic practices like betel quid chewing, patterns of use of alcohol and tobacco contribute to increasing incidence of oral cavity malignancies in these parts of the world.

As per the Globocan 2012 fact sheet the incidence and prevalence of oral cavity cancer is more in men than women as shown below (2).The increased use of tobacco and alcohol in men directly reflects in the gender ratio statistics.

Estimated incidence, mortality and 5-year prevalence: women

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	101398	1.5	2.5	47413	1.3	1.2	234992	1.4	9.1
Nasopharynx	25795	0.4	0.7	15075	0.4	0.4	66799	0.4	2.6
Other pharynx	27256	0.4	0.7	18507	0.5	0.5	58873	0.3	2.3
Oesophagus	132776	2.0	3.1	118952	3.4	2.7	127528	0.7	4.9
Stomach	320301	4.8	7.5	254103	7.2	5.7	507340	3.0	19.5
Colorectum	614304	9.2	14.3	320294	9.0	6.9	1590151	9.3	61.2
Liver	228082	3.4	5.3	224492	6.3	5.1	179825	1.0	6.9
Gallbladder	101257	1.5	2.3	82484	2.3	1.8	115278	0.7	4.4
Pancreas	159711	2.4	3.6	156564	4.4	3.4	97110	0.6	3.7
Larynx	18775	0.3	0.5	10115	0.3	0.2	53082	0.3	2.0
Lung	583100	8.8	13.6	491223	13.8	11.1	626382	3.7	24.1
Melanoma of skin	111481	1.7	2.8	24098	0.7	0.6	417080	2.4	16.1
Kaposi sarcoma	15225	0.2	0.4	9616	0.3	0.3	25058	0.1	1.0

Estimated incidence, mortality and 5-year prevalence: men

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	198975	2.7	5.5	97940	2.1	2.7	467157	3.1	18.0
Nasopharynx	60896	0.8	1.7	35756	0.8	1.0	161899	1.1	6.2
Other pharynx	115131	1.6	3.2	77598	1.7	2.2	251118	1.6	9.7
Oesophagus	323008	4.4	9.0	281217	6.0	7.7	336535	2.2	13.0
Stomach	631293	8.5	17.4	468970	10.1	12.8	1030787	6.7	39.7
Colorectum	746298	10.1	20.6	373639	8.0	10.0	1953431	12.8	75.3
Liver	554369	7.5	15.3	521041	11.2	14.3	453345	3.0	17.5
Gallbladder	76844	1.0	2.1	60339	1.3	1.6	90368	0.6	3.5
Pancreas	178161	2.4	4.9	173827	3.7	4.8	114434	0.7	4.4
Larynx	138102	1.9	3.9	73261	1.6	2.0	388593	2.5	15.0
Lung	1241601	16.8	34.2	1098702	23.6	30.0	1266696	8.3	48.8
Melanoma of skin	120649	1.6	3.3	31390	0.7	0.9	452674	3.0	17.4
Kaposi sarcoma	29022	0.4	0.8	17358	0.4	0.5	55337	0.4	2.1
Prostate	1094916	14.8	30.7	307481	6.6	7.8	3857500	25.2	148.6

Fig 3: Gender wise comparison global Incidence, mortality and 5-year prevalence of various cancers

Disease burden in India

In a developing country like India, the epidemiology of oral cavity cancer is different when compared to a developed western population(4) .When compared to United States of America where oral cavity cancers constitute to 3% of all malignancies; in India it comes around 30 % of all malignancies. The regional variation in prevalence of risk factors and various cultural factors is the main cause for this geographical variation in the incidence and prevalence of disease(5).According to ICMR, oral cavity cancers comprise more than 50 % of all head & neck cancers(4). In India, the age standardized incidence rate of oral cancer is 12.6 per 100,000 population(6). The In addition to exposure to tobacco, alcohol various other factors like low economic status, late diagnosis due to poor accessibility to health care facilities and low literacy play an

important role in increase in incidence rate compared to Western countries. The age standardized incidence in males very high compared to female as shown in the graph below.

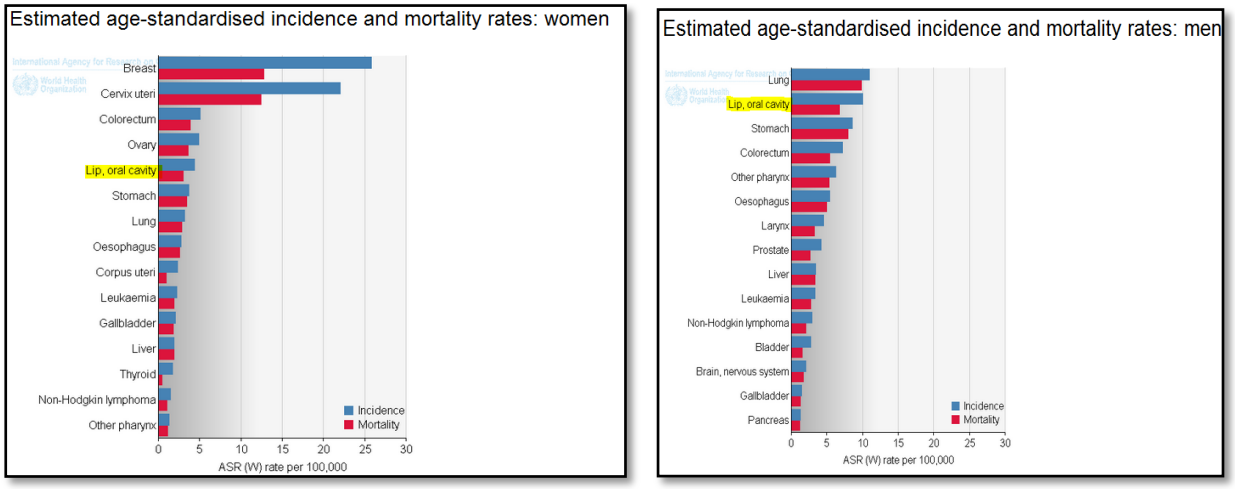


Fig 4: Gender wise comparison of Incidence, mortality and of various cancers in India

Regional Scenario

According to population based cancer registry of Chennai relative proportion of oral cavity cancer constitute about 10.8% and 5.9% in males and females respectively(7). Age standardized incidence rate of oral cavity cancer in Chennai is 18.6 per 100,000 population(8).

Risk factors

The major risk factors contributing for the development of oral cavity cancers are Tobacco and alcohol consumption (9).HPV infection, dietary factors and constant oral irritants are the various other causes of oral cavity cancer.

Tobacco: is the major risk factor which contributes about 41% of oropharyngeal cancers in men and 15% in women .Tobacco is consumed in various ways and which can be broadly classified as

Smokeless Tobacco

Smoking Tobacco

Smokeless Tobacco includes using tobacco in the form of chewing, snuff, gutka, snus, masheri. Snus means tobacco powder mixed with salt and sodium carbonate and is typically kept under lips. Masheri is burnt tobacco powder used to clean teeth.

Smoking Tobacco is used in the form of cigarette, cigars, pipes, beedi, kretek and hookahs. Beedi is made by rolling tobacco in a dried leaf from the tendu tree. Kretek is a cigarette made with a mixture of tobacco and cloves. A hookah is a device used to smoke tobacco in which smoke passes through a partially filled water bowl before being inhaled by the smoker. There are approximately 250 chemicals entering the body during

smoking and among these 70 of are potential carcinogenic substances(10).The most common carcinogens causing oral malignancy are nitrosamines, polycyclic aromatic hydrocarbons and amines(11).

Various modalities of use of tobacco use is found to have synergistic effect in causation of cancer (3). Reverse smoking will lead to heat related alteration of palatal mucosa known as "reverse smokers' palate "which is at high risk of malignant transformation. The quantification of cigarette smoking is done by using pack years.

$$\text{No. of pack-years} = \frac{\text{No. of cig. smoked per day} \times \text{no. of years smoked}}{20}$$

Alcohol: Consumption of alcohol is much pronounced as a causative factor for oral cancer when it is used along with smoking. Smoking along with alcohol consumption doubles the risk of development of oral cavity cancer(12).Ethanol acts as an initiator of carcinogenesis or as a promoter which will increase the permeability of environmental carcinogens into the cell. Alcohol dehydrogenase oxidize ethanol to acetaldehyde and which is a potent carcinogen causing oral cavity cancers(13).

Role of HPV: Epidemiological studies on etiological factors of cancer showed though there is decrease in use of tobacco products it was not translated into decrease in number of head and neck cancers(14).

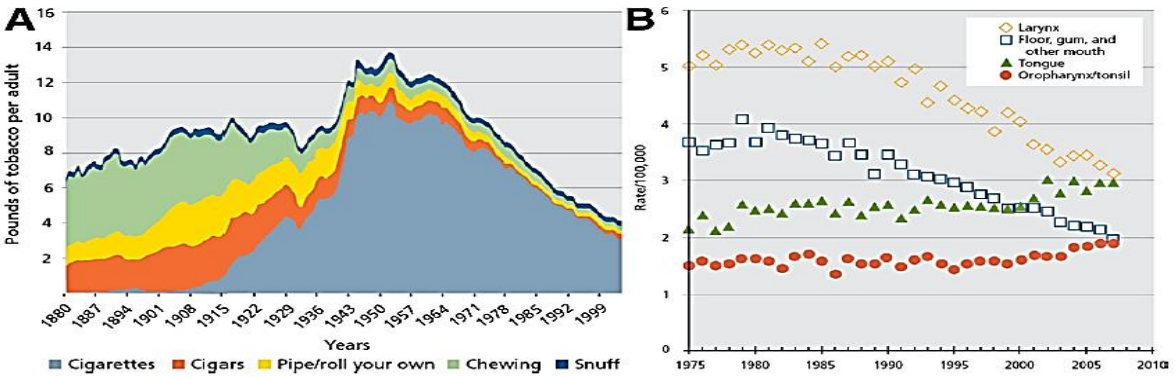


Fig: 5Epidemiological Shift

This lead to the researchers to investigate for other factors contributing for head and neck cancers. Hobbs et al studied association between hpv16 and head and neck cancer and the relationship was found to be strongest for the tonsils with an odds ratio:15.1 and was weak for oral cavity and larynx with odds ratio of 2(15). HPV positive cancers are clinically and molecularly distinct from HPV-negative cancers and with different risk factor profiles(16)(17).

Table 1 HPV Negative versus Positive

Feature	HPV-negative	HPV-positive
Age	Above 60 years	Middle-aged
Risk factors	Tobacco +/- alcohol	Sexual behaviour
Field cancerization	yes	Unknown
Predilection site	None	Oropharynx
T stage	Higher T Stage	Lower T Stage
Nodal status	Lower	Higher
TP53 mutations	Frequent	Infrequent

HPV positive cancers was found have good prognosis than HPV negative cancers. Various theories has been proposed for the improved outcomes in patients with human papilloma virus-positive cancers which include the presence of viral- specific antitumor immunity, wild-type p53, alterations in tumor microenvironment leading to improved tumour oxygenation(18).

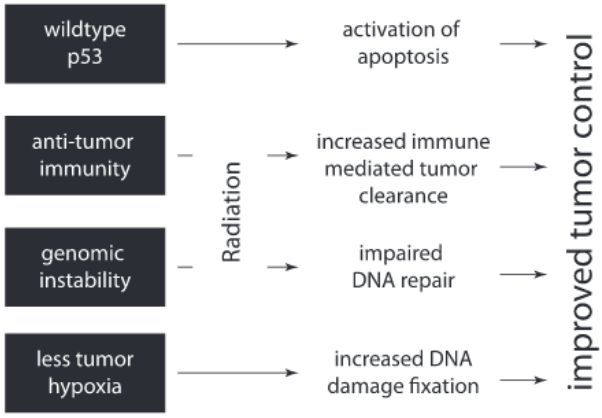


Fig6:Probable Mechanisms which leads to improved outcomes in human papilloma virus-positive squamous cell carcinoma of the head and neck(19)

Other Factors: Absence of vegetables and fruits in diet with a high fat or sugar intake can act as a contributing factor for oral cavity cancer(19).Chronic irritants like sharp tooth, pan also can also lead to oral cavity cancer

Precancerous lesions and role of screening

As per WHO Premalignant lesion is defined as a morphologically altered tissue in which cancerous change is more likely to occur if it is left untreated than its apparently normal counterpart. Precancerous lesions like oral leukoplakia , erythroplakia and oral submuous fibrosis contribute to 30 to 80% of oral cavity cancers(20). Leukoplakia is defined as a white patch or plaque that cannot be characterised clinically or pathologically as any other disease. Leukoplakia is diagnosis of exclusion. Erythroplakia presents as bright red velvety plaques which cannot be characterised clinically or pathologically as any other recognisable condition.

Table 2 Premalignant lesions

Type	Risk of malignancy
Erythroplakia	90-100%
Leucoplakia	15.6 -39.2%
Oral submucosal fibrosis	3-6%
Actinic keratosis	0.025 -16%

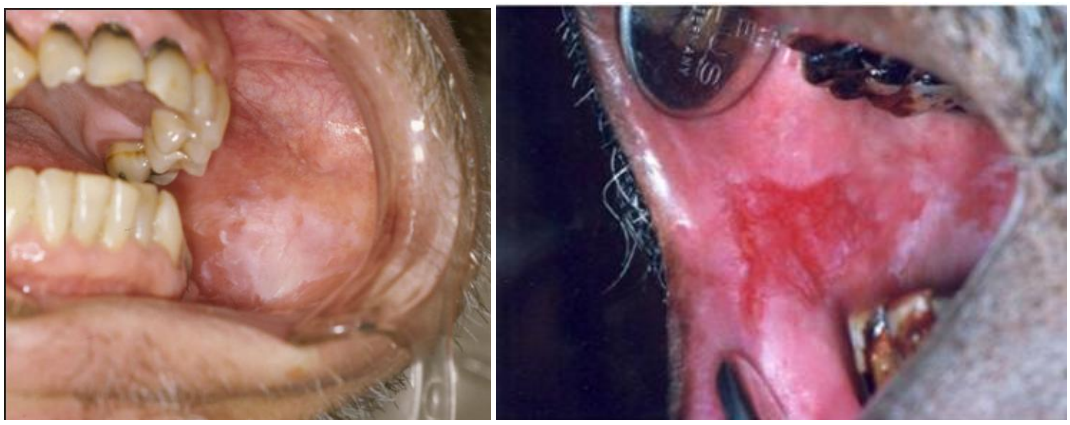


Fig 7 Oral Leukoplakia and Erythroplakia(20)

Role of screening in oral cavity malignancies

According to WHO oral cancer screening examination should include a visual inspection and palpation of all sub sites of oral cavity and face with help of mouth mirrors. The examination is not complete without palpating the regional lymph nodes, tongue, and floor of the mouth. Any abnormality that lasts for more than 2 weeks should be revaluated and considered for biopsy. The United states Preventive Services Task Force recommends that in asymptomatic adults current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer but at the same time screening of high risk group who used tobacco or alcohol had resulted in reduction the mortality rate from oral cancer(21)

Gross anatomy

Oral cavity is the beginning of aero digestive tract and it starts at vermillion border and it leads into the oropharynx. The roof of the mouth is formed by the hard palate and side walls by buccal mucosa. The borders of the oral cavity are

Anterior : lips

Inferiorly: mylohyoid muscle, alveolar ridge of mandible and teeth

Lateral : gingivobuccal mucosa

Posterior : circumvallate papillae, tonsillar pillars and soft palate

Superior : hard palate and maxillary alveolar ridge and teeth,

The sub sites of oral cavity include:

Lips

Labial mucosa

Vestibule oral tongue (the anterior two-thirds of the tongue)

Floor of the mouth

Buccal mucosa

Gingiva

Retromolar trigone

Hard palate

Teeth

Lower jaw

Upper jaw

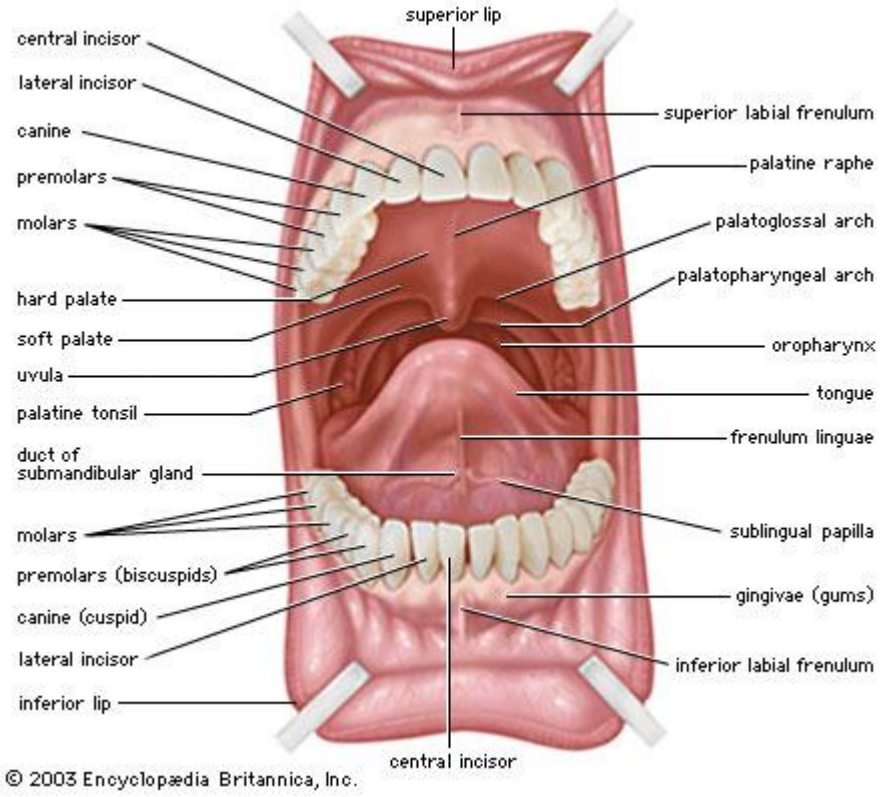


Fig 8 : Oral cavity Anatomy

Staging of oral cavity malignancy

The assessment of the primary tumour and the draining neck nodes is based on clinical examination, indirect mirror examination and nasopharyngolaryngoscopy. Histopathological confirmation of the tumour is mandatory .Most common histological type is squamous cell carcinoma. Locoregional imaging includes magnetic resonance imaging or computed tomography of head and neck .The metastatic work up includes chest X-ray .

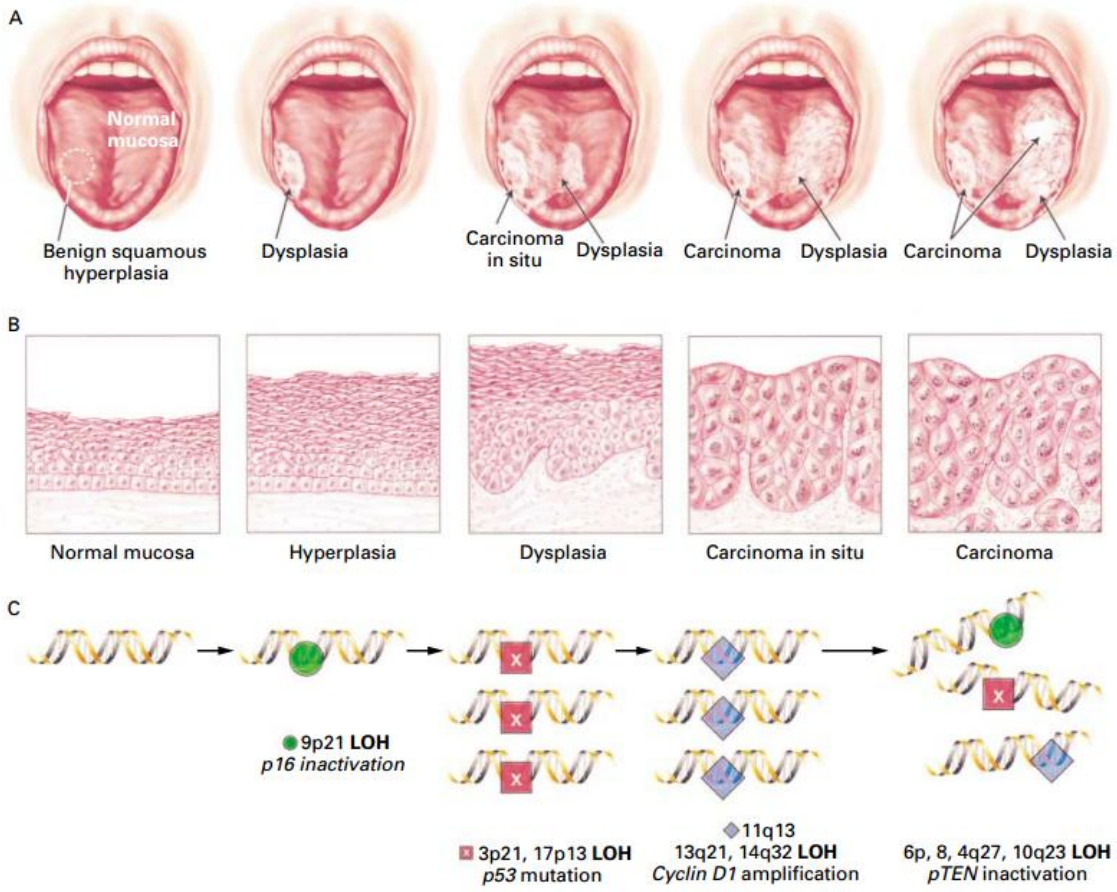


Fig 9: Clinical, Pathological and Molecular Progression of oral cancer(23)

Oral cavity malignancies are staged according to the Tumour Nodes Metastasis (TNM) classification of the Union against Cancer and the American Joint Committee on Cancer (seventh edition)(24).

The T component is defined by the size or contiguous extension of the primary tumour.

The N component is defined by the absence, or presence and extent of cancer in the regional draining lymph nodes.

The M component is defined by the absence or presence of distant spread or metastases, generally in locations to which the cancer spread by vascular channels, or by lymphatic beyond the nodes defined as “regional.”

TNM STAGING

Primary Tumor (T)

Oral cavity

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T is Carcinoma in situ

T1 Tumor 2cm or less in greatest dimension

T2 Tumor more than 2cm but not more than 4 cm in greatest dimension

T3 Tumor more than 4 cm in greatest dimension

T4a (Lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose

T4a (Oral Cavity) Tumor invades through cortical bone, into deep [extrinsic] muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face

T4b Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension

N2a Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Table 3: Staging of Oral cavity(24)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IVB	T Any	N3	M0
IVC	T Any	N Any	M1

Symptoms in Oral cavity cancer

.Early symptoms of oral cavity cancer include a

- nonhealing ulcer
- Swelling or thickening of mucosa of oral cavity
- Loose teeth and ill-fitting dentures
- Fetor and persistent foreign body sensation
- Painful swallowing
- Whitish or reddish patch in oral cavity.

It may be associated with general symptoms like fatigue, pain, weight loss or bleeding. In advanced stage, according to the anatomical structures the tumour has infiltrated and spread to other organs ,it can cause various symptoms as depicted in the table below.(27, 28).All the above mentioned symptoms are very subtle and most of time patients either ignore the symptoms or undergo treatment with short course of analgesics, antibiotics, over the counter medication or with Alternative Medical Therapy. This leads to delay in diagnosis and most of the patients present in locally advanced stage. Here lies the importance of screening programmes and training general practitioners in identifying the warning signs and symptoms at an early stage

Table 4 Common routes of spread of oral cancer (22)

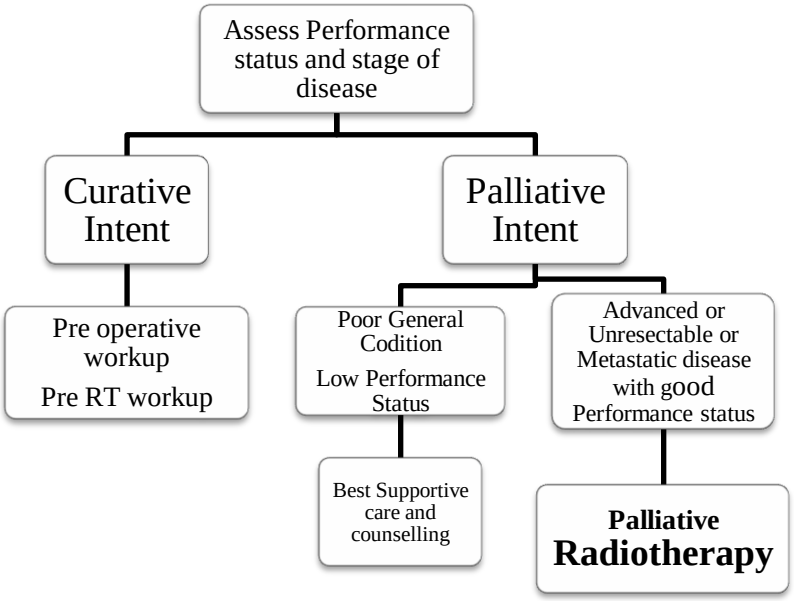
Tumour site	Routes of spread	Symptoms
Tongue	Intrinsic and extrinsic musculature, neurovascular bundle, floor of mouth, mandible	Speechdifficulties,ankyloglossia
Retro molar trigone	Mandible,pterygomandibular raphe,buccinator and superior constrictor muscle or paranasal sinus	Loosening of the teeth, pain around the teeth ,nasal regurgitation, trismus
Lip	Orbicularis oris, skin, buccal mucosa, mandible/maxilla	Ulcer, swelling
Floor of mouth	Submucosal spread, invasion of lingual neurovascular,bundle/extrinsic tongue musculature, mylohyoid and hyoglossus muscles, mandible	Restriction of Tongue movements, stiffness of jaw
Palate	Osseous erosion of hard palate, greater and lesser palatine nerves ,Paranasal sinus,Pterygopalatine fossa	Numbness of the tongue, teeth, or lips, voice changes

Treatment modalities in Oral cancer

General Principles:

Guidelines of treatment planning of advanced oral cavity cancers are derived from trials that included a heterogenous group of patients which included all head and neck sites and observational data from oral cavity cancer patient series. Hence decision regarding optimal integration of surgery, radiation and chemotherapy should be made on case to case basis in a multidisciplinary tumour board setting. Ideally all patients should be seen by the surgeon, radiation oncologist, and medical oncologist prior to final decision making of treatment strategy. The individualised management plan is made in multidisciplinary tumour board taking into account the various tumour factors, patient factors and functional outcomes of treatment, as well as the expertise of the treatment team and availability of treatment delivery techniques. General approach for any head and neck cancer is shown below

Decision on Intent of Treatment



Early oral cavity cancer (stage I and II) are treated with single modality surgery or brachytherapy withsimilar 5 year survival rates of 80-85%.But majority of oral cavity cancers in India present in locally advanced stage which warrants multimodality treatment. This is in view of highly aggressive biologic nature and high rates of local recurrence noted after treatment with surgery or radiotherapy alone. Hence combined modality treatment which includes surgery followed by radiotherapy with or without chemotherapy is the preferred approachoperable stage III and stage IV disease.

Role of Surgery in Oral cavity Cancers

Surgical excision is the recommended as the initial therapy for locally advanced oral cavity cancers if simultaneous resection and reconstruction is feasible with acceptable functional outcomes. The factors to be kept in mind before embarking withsurgery are the likelihood of the surgeon achieving adequate surgical margins, acceptable morbidity after

reconstruction, good functional outcome in terms of speech and swallowing, which will affect quality of life. These issues have to be discussed in detail with the patients prior to surgery. R classification divides the types of surgery based on clinical and pathological findings as R0, R1 and R2 which means complete resection without any microscopic evidence, microscopic residual tumour and macroscopic residual tumor respectively

Surgical management includes three major subdivisions:

1. Treatment of Primary
2. Treatment of Neck
3. Reconstruction

Treatment of Primary (Sub site wise)

LIP: For T1, T2tumors, single modality treatment in the form of wide local excision with aim ofachieving of negative margins of 0.5cm to 1cm all around the tumour. Alternatively, radical radiotherapy or brachytherapy can be offered as the treatment of choice. ForT3, T4 tumors surgery and subsequent postoperative radiotherapy with or without chemotherapy is the treatment of choice. Chemotherapy is added based on the surgical histopathological findings. In T3, T4 lesions wide excision with resection of mandible which can be marginal mandibulectomy or segmental or hemimandibulectomy with reconstruction is preferred surgery

BUCCAL MUCOSA: For T1, T2 tumors surgery of choice is wide localexcision with or without marginal mandibulectomy with reconstruction. Radical external beam radiotherapy and Brachytherapy are other options. For T3, T4 tumors composite resection of the buccal mucosa with mandible or upper alveolus or overlying skin with reconstruction followed by adjuvant radiotherapy with or without chemotherapy is the preffered treatment

ORAL TONGUE & FLOOR OF MOUTH: For tumors less than 5 cms surgical option is Wide excision Glossectomy or Hemiglossectomy with appropriate reconstruction. Radical radiotherapy in the form of external beam radiotherapy or brachytherapy is another alternative for T1 and T2 tumors. For Tumors more than 5 cms wide excision glossectomy with mandibular swing or pull through along with lingual plate or segmental or hemimandibular resection with reconstruction is the preferred surgery with adjuvant therapy based on histopathological examination

LOWER ALVEOLUS & RETRO MOLAR TRIGONE: If mandible is uninvolved or minimally involved wide excision with marginal mandibulectomy is the procedure of choice especially when there is minimal periosteal invasion or there is only superficial bony erosion. But if there is gross involvement of the bone or else patient is edentulous or gross paramandibular disease or prior radiation exposure segmental or hemimandibulectomy is preferred over marginal mandibulectomy. Post operative adjuvant treatment with radiotherapy or chemo radiotherapy is decided on risk factors in the histopathological examination report.

Treatment of Neck

Management of N0 Neck

Management of node negative neck in oral cavity cancers is still not clear. For tumors less than 5cms the options of management include either observation or Supraomohyoid neck dissection (SOHND).SOHND is indicated if high grade tumor or tumor thickness more than 4 mm or a non complaint patient for follow up or T3, T4 lesion. SOHND should be ideally followed by frozen section and modified radical neck dissection if frozen section is positive.

Radical or modified radical neck dissection is indicated in node positive neck and bilateral neck dissection is indicated in a midline primary tumor or tumor crossing midline.

Role of Reconstruction

The aim of reconstructive procedures in oral cavity include to facilitate healing and covering of the surgical defect, to reduce post operative morbidity by preventing aspiration and preserving swallowing function and speech .Reconstruction procedures also aim at filling the defects in skin, mucosa and bone and thereby help in attaining good cosmesis. Local flap, free flap, Pectoralis Major Myo Cutaneous flap (PMMC) are various options for reconstruction of skin and mucosa. Free fibula graft cadaveric bone graft and silastic plate are the different bone reconstruction techniques used during surgery of oral cavity tumors.

Role of Induction Chemotherapy:

Although there is a strong rationale for induction chemotherapy which would lead to surgery with good functional preservation, the toxicity profile which might lead to patient status unfit for any definitive treatment restricts the use of this strategy as first-line treatment. There is lack of literature showing any overall survival benefit by induction chemotherapy approach also discourages the rampant use of neoadjuvant chemotherapy. This can be considered as a feasible option in selected scenarios like delay in surgery or borderline operability of the primary.

Role of Radiotherapy or chemoradiotherapy in adjuvant setting

Adjuvant therapy with radiation alone or chemoradiation is based on results of histopathological examination of the surgical specimen. According to EORTC and RTOG trials absolute indication for adjuvant chemo radiation is indicated for positive margins and extracapsular extension. Adjuvant radiotherapy is indicated in head and neck cancers if high risk features like lymphovasular invasion, perineural invasion,more than two involved neck nodes,nodal diameter>3 cm, Invasion of bone, cartilage, skin or soft tissue of the neck or an advanced T stage, Tumor spillage. Oral cavity as primary itself is considered as high risk factor.

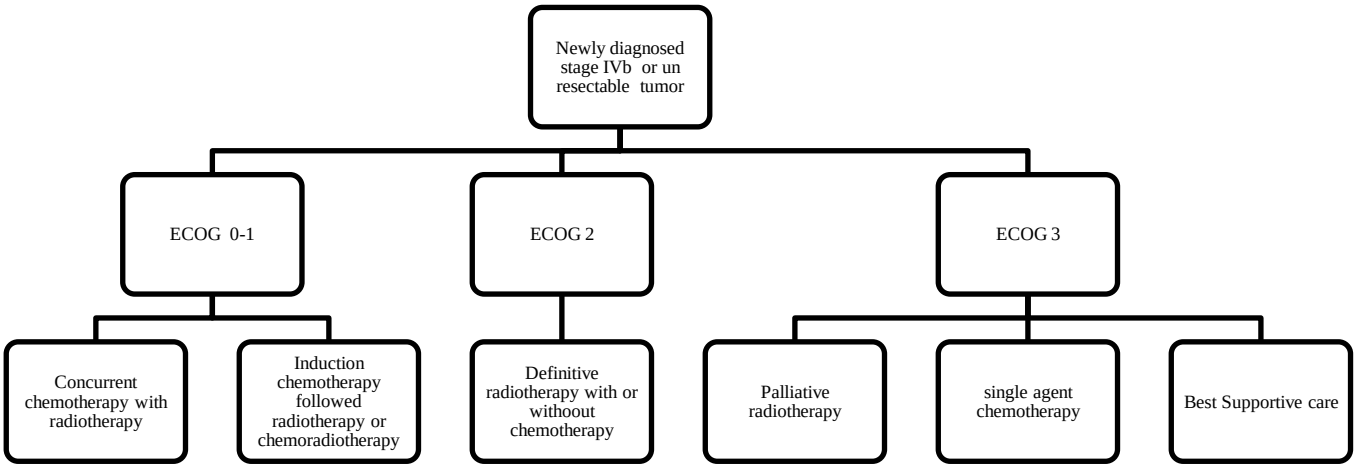
Minimum dose should be 60 Gy in 1.8-2Gy per fraction in postoperative radiation. Uninvolved lower neck should be treated with a minimum dose of 50Gy. The dose should be escalated to 66Gy in high risk areas.

From the above discussion it is clear that combined modality treatment with surgery followed by adjuvant therapy is the preferred strategy in local advanced oral cavity cancer. Though surgery is the first option in most of the cases,surgically , R0resection is technically not possible without affecting functional outcome if the primary tumour invades infra-temporal fossa and masticator space or extensive skull base involvement or extensive induration or soft issue involvement till zygomatic bone or hyoid bone or severe trismus. Hard and fixed N3 nodes or extensive skin involvement or infiltration of carotid vessels or prevertebral muscle renders these patients technically inoperable(4).In these situations, the intent of treatment changes from curative to palliative in intent.

In short any cancer in oral cavity which is technically unresectable with best reconstruction should be approached with a combined modality of treatment with chemotherapy and radiotherapy. If a positive cut margin or R1 or R2 resection is expected post surgery which warrants adjuvant postoperative chemoradiotherapy it's advised to avoid surgery since survival outcomes are poor.In such cases concurrent chemoradiotherapy or radiotherapy with cetuximab is considered if patient has good performance status and primary is borderline inoperable or in other words salvage surgery can be offered after the combined modality treatment. The drug preferred for concurrent chemotherapy is cisplatin. The recommended dose is cisplatin 30 mg/m2 weekly or 100 mg/m2 every three weekly . Minimum cumulative dose recommended is 200 mg/m2.But if performance status of patient is poor or if patient cannot tolerate

combined modality and salvage surgery option cannot be offered after chemoradiotherapy , palliative radiotherapy is the next option.

Both National Comprehensive Cancer Network Guidelines (NCCN) and Consensus of recommendations for management of head and neck cancer in Asian countries offers almost similar treatment options for very advanced head and neck cancers as follows:



Palliative radiotherapy regimens are different from standard definitive radiotherapy regimens which use 2Gy per fraction for five days a week for 30 to 35 fractions depending on adjuvant or radical setting .In Palliative radiotherapy the main aim of treatment is symptom control than cure. So hypofractionated regimens are preferred where overall treatment time will be less and dose per fraction will be high.

Radiobiological explanation of hypofractionated radiotherapy

Hypofractionation is an alternative fractionation schedule in which use of high doses per fraction (usually > 2.2Gy) with less number of total fractions. Tumour control probability is slightly decreased in view of low dose(38).Acute side effects are comparable to conventional. Since dose per fraction is high late effects will be more compared to conventional fractionation. The issue of late toxicity won't affect much since hypofractionated radiotherapy is advocated in palliative setting where overall survival is low. Other situations where hypofractionation is used are for tumours with low α/ß like melanoma, liposarcoma and prostate carcinoma.

Advantages of hypofractionated regimen is that overall treatment time is less(39).It is known that palliative radiotherapy schedules should be designed in such that the treatment duration is kept as short as possible. It helps in well utilization of machine time. Radiobiological explanation for this concept is the treatment should be completed before the commencement of accelerated repopulation(40).

The concept of accelerated repopulation also stress upon the importance of delivering maximum tolerable dose in short span of time with consideration to toxicity in a palliative setting. Accelerated repopulation refers to the triggering of surviving cells (clonogens) to divide more rapidly as a tumour shrinks after irradiation or treatment with any cytotoxic agent. Accelerated repopulation starts in head and neck cancer in humans about 4 weeks after initiation of fractionated radiotherapy(40). About 0.6 Gy (60 rad) per

day is needed to compensate for this repopulation. This phenomenon mandates that treatment be completed as soon as possible once it has started. This concept also signifies the importance of avoiding breaks in between treatment once it is started.

Overall treatment time is a very important factor for oral cavity malignancy as it is a fast growing malignancy. In head and neck cancer, local tumour control is decreased by about 1.4% (range 0.4-2.5%) for each day that the overall treatment time is prolonged. The corresponding figure for carcinoma of the cervix (another cancer site common in India) is about 0.5% per day. Such rapid proliferation is not seen in breast or prostate cancer.

Concept of fractionation and Biological effective dose

The basic principle of radiation therapy is to deliver maximum dose to the tumour and at the same time to make sure that surrounding normal tissues get minimum dose. Total dose cannot be given in single dose because this will produce serious adverse effects to normal tissues.This idea of a compromise between local tumour control and the development of complications gave rise to the concept of a therapeutic ratio. Therapeutic ratio is the ratio of the dose that leads to serious complication in 50% of patients, to the dose that gives tumour control in the same 50% of patients(29).

Studies in radiotherapy were going on in early 20th century with the aim of improving therapeutic ratio and thus came the idea of using fractionation in radiotherapy. The concept of fractionation in radiotherapy started in 1920's after the experiments in Ram done in France. Fractionation means dividing the total dose into number of fractions(29)

.Fractionation allows normal tissue to recover &repair sub-lethal damage due to previous fraction. Radiobiologicaly how fractionation improves therapeutic ratio can be explained by 4 Rs'(30).

4 Rs' of Radiobiology(30,31):

1. Repair

2. Reassortment

3. Repopulation

4. Reoxygenation

Repair

Radiation induced damage in a mammalian cell can be classified into:

a) Lethal damage

b) Potentially lethal damage

c) Sublethal damage:

Lethal damage is irreversible and irreparable and causes cell death. Potentially lethal damage describes the radiation damage which can be altered by environmental factors into lethal damage after radiation. Sublethal damage is the radiation damage which can be repaired in hours unless another sublethal damage occurs. So if we split a dose of radiation into two fractions or separated by a time interval we can increase the survival of normal cells by repairing the sublethal damage(30).Repair is the mechanism by which the function of DNA is restored(30).Two theories explain repair of radiation induced sublethal damage(30).

1) Template Theory: As shown in the picture below the base pair are complimentary in normal DNA helix (figure 10A).Figure 10B shows in single strand break repair occurs using other helix as template. And if double strand break occurs at different level, repair will be done as two different single strand break (figure10 C). Double strand break facing each other will not be repaired and lead to cell death(figure 10D)(29).

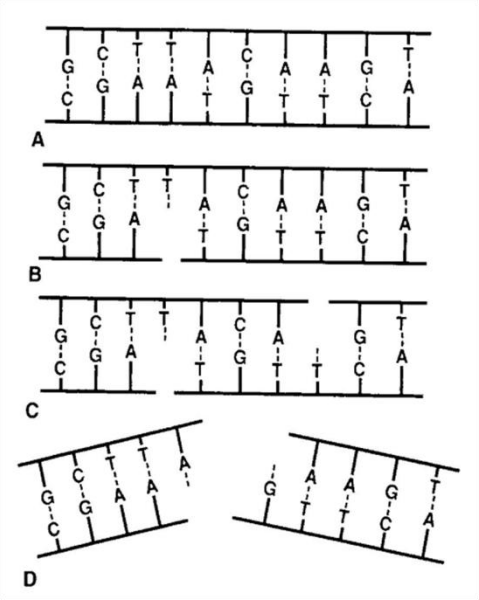


Fig 10: Types of DNA breaks

2) Chemical pool theory:

Chemical pool theory proposes there are multiple targets in the cell. If we consider there are N targets and all targets are hit simultaneously then all the sublethal damage effect will accumulate and causes a lethal damage. But if (N-1) targets were hit repair of the sublethal damage will occur instead of cell death. Based on this Elkind & Sutton showed that when two exposures were given two hours apart the shoulder reappeared on cell survival curve repair of (N-1) target will take place(29).

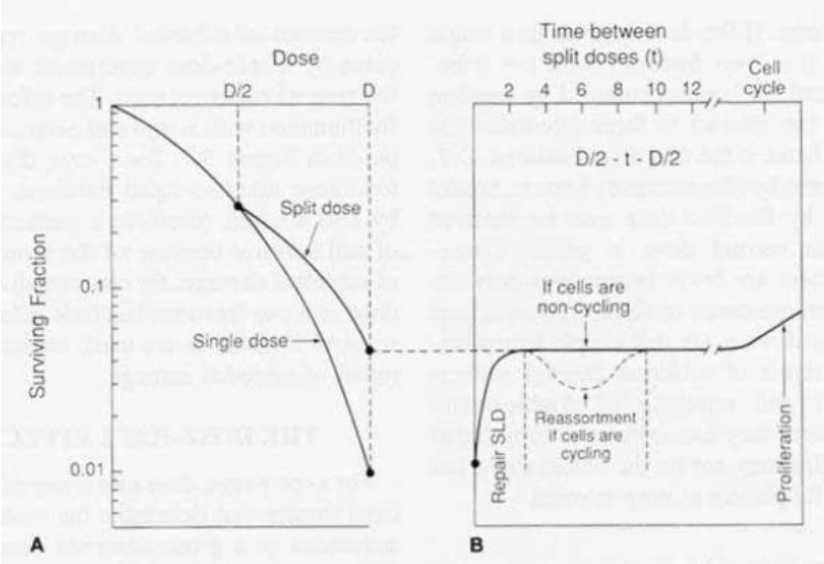


Fig 11: Relationship between surviving fraction and Fractionation

Reassortment

The radio sensitivity of cells varies considerably as they pass through the cell cycle.

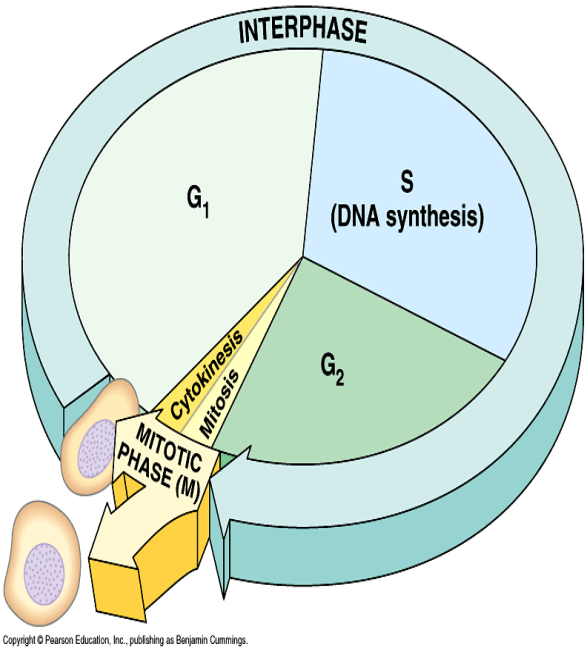


Fig 12: Phases of Cell cycle

As depicted in figure 12, 'S' phase is the most radio resistant phase of cell cycle and 'G-2' phase is the most radiosensitive. During fractionation of dose, cells in sensitive phase are killed and before next fraction, cells progress through cell cycle and again come to sensitive phase. This process is known as redistribution or reassortment(31)

Repopulation

During an extended course of radiotherapy cells that survive irradiation may proliferate faster and thus increase the number of cells that must be killed.

Reoxygenation

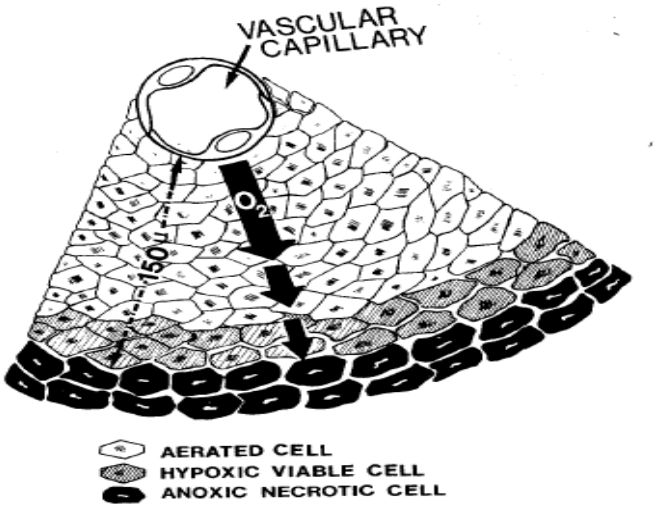


Fig 12: Different types of cell depending on exposure to oxygen

As shown in the figure 12 any sheath of tumour contain three zones. Cells that survive the first dose of radiation will tend to be hypoxic and radioresistant. After death and loss of other tumour cells due to previous irradiation the surviving cells become more radiosensitive as they are more exposed to oxygen by coming into closer proximity to capillaries(31).

In short dividing a dose into a number of fractions spares normal tissues by repair of sublethal damage and repopulation. At the same time it increases damage to tumour by reoxygenation and reasssortment.

Effect on radiation on tissues

The effect of radiation on tissues as a function of dose is measured by assays and it is represented with cell survival curve. All normal tissues do not have similar effect to tissues. There is clear distinction between early responding (skin, mucosa, intestinal epithelium) & late responding (spinal cord) tissues(32).

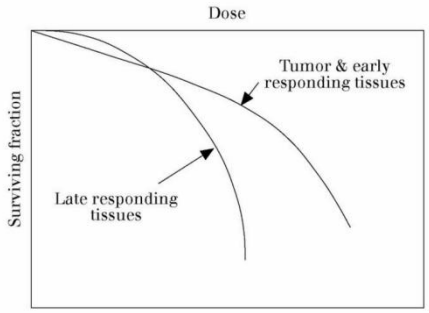


Fig 13: Dose response curve for different types of tissues

Linear Quadratic Model explains about different responses between tumour, early responding and late responding tissues. The tumour and early responding tissues like skin and mucosa respond similar to radiotherapy. The dose-response relationship for late responding tissues is more curved than that for early responding tissues(33).

The time after the start of a fractionation regimen at which extra dose is required to compensate for cellular proliferation is quite different for late as opposed to early responding tissues. Hence prolonging overall treatment time within the normal

radiotherapy range has no sparing effect on late reactions but a large sparing effect on early reactions. By prolonging overall time it will help in sparing of normal tissue reaction of early responding tissues but it will not have any sparing effect on late reactions(33,34).

The dose survival curve becomes exponential from linear if radiation is delivered in multiple fractions with fixed time interval gapinstead of single fraction as shown in Fig 15.The reason behind this is time interval allows sublethal damage repair and the shoulder of the curve is repeated again and again(35).

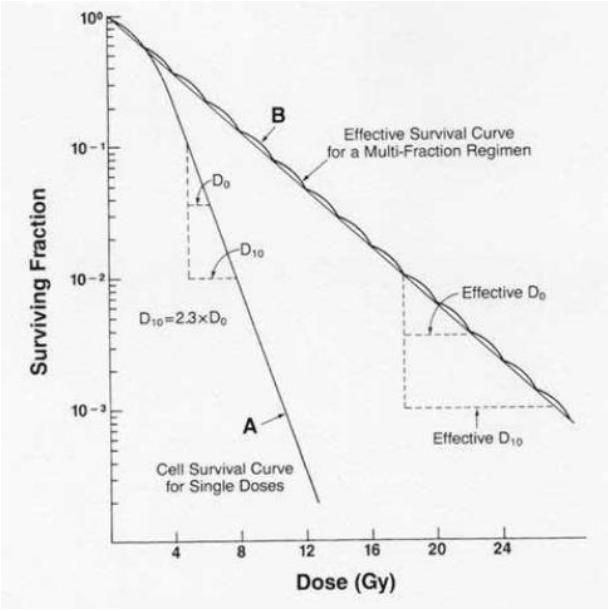


Fig 14: Cell survival curve for single fraction versus multiple fractions

Various radiobiological Models have been proposed to explain the effect of fractionation. The major ones are

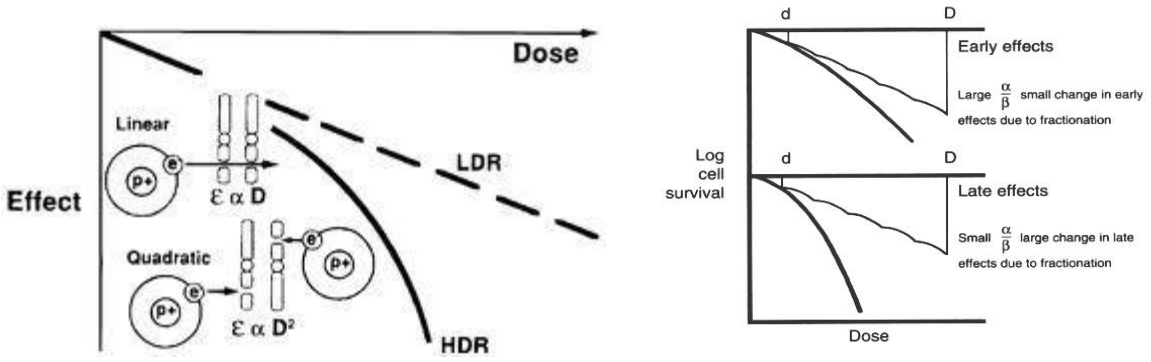
a) Strandqvist Plot

b) Nominal Standard Dose System (NSD)

c) Linear - Quadratic Model

The most accepted theory is Linear Quadratic model which was proposed by Fowler and Stern in 1960's.This concept was expanded by Barendsen and Dale in 1980's(34).

The Linear - Quadratic Model is a mechanistic and biologically based model which assumes radiation cell kill is based on double strand DNA damage. It explains double strand DNA damage can occur by two ways. Type A damage means single ionizing radiation causing double strand breakage. Type B damage means two separate complimentary ionizing radiation causing double strand breakage. In type B damage second ionizing radiation should hit within few base pair near first radiation and it should occur before the time of repair of first ionizing radiation. As depicted in the figure 15 LQ model explains that radiation induced cell kill has a linear component and quadratic component(35).



The initial linear component (αD) is due to single track of event.The quadratic component (ßD2) which is due to double track of events.

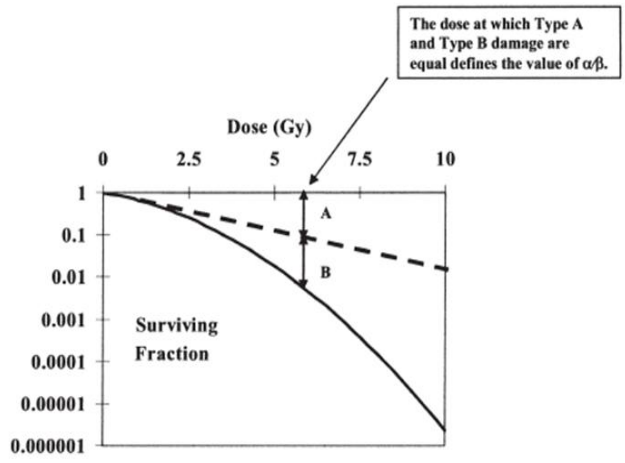


Fig 15: Linear quadratic model

S = exp -(αD + ßD2)

α is the initial slope of the line of the line at dose 0

ß is the downward curvature of solid line at higher doses

Linear quadratic model explains radiobiology of cell with the help of above equation and variables. The dotted straight line indicated the linear component or type A damage. Deviation of the survival curve from the straight line indicates the extra lethality caused by type B damage.

S is the fraction of cells surviving the dose D. The literal interpretation of α/ß is for a given tumour or organ, the physical dose at which the two types of biological damage (Type A and Type B) are equal. Type A damage predominates at dose of radiation is less than α/ß of the tissue, whereas at higher doses of radiation, type B damage predominates. Tissues possessing a small α/ß have more sparing capacity than those with higher values. This means that, for any given dose, the reduction in cell kill brought about by a reduction in dose per fraction or dose rate will be relatively greater in low α/ß tissues(36). In terms of linear quadratic relationship for early effects α/ß is large and α dominates at lower doses the dose response curve has a marked initial slope and dose not bend till higher doses. For early responding tissues linear and quadratic cell killing will be equal by about 10Gy. For late effects α/ß is small and dose response curve bends at lower dose and linear and quadratic cell kill will be equal by about 2Gy.

The "Standard Fractionation" for radiotherapy has evolved as 5 fractions a week by empiricism and convenience. Other alternative fractionation schedules are(32)

1. Hyperfractionation
2. Accelerated Fractionation
3. CHART
4. Hypofractionation
5. Split Course

Table 5 Alternative fractionation schedules

Altered Fraction	Overall Time	Dose per fraction	No. of fraction	Total Dose	Intent
Hyper Fraction	Same	↓	Doubled/ More	↑	Tumor Control: Same/ Better Acute Effects: Slightly more Late Effects: Less
Accelerated Fraction	↓	Same	Same; but 2-3 # per day	Same	Tumor Control: Better Acute Effects: Pronounced Late Effects: Same
CHART	↓↓	Same	Same	Same	Tumor Control: Better Acute Effects: Pronounced Late Effects: Same
Hypo Fraction	↓	↑	↓	↓	Tumor Control: Poor Acute Effects: Less Late Effects: High
Split Course	↓	↑	↓	↓	Tumor Control: Poor Acute Effects: Less Late Effects: High

In order to compare biological effects of various fractionation schedules the concept of Biologically effective dose(BED) came into existence. Biologically effective dose (BED) is a measure of true biological dose delivered by a particular combination of dose per fraction and total dose to a particular tissue.BED helps in converting physical dose into a dose that describes the biological effect of the radiation on tumour or normal tissue(37) .BED is a quantity with unit Gy defined as

$BED = E/\alpha = nd\ (1 + d\text{—— } \alpha/\beta)$

n is the number of fractions,

d is dose per fraction expressed in Gy

α and β are parameters that determine the linear and quadratic components of the dose response.

E is the biological effect which is expressed by (*αnd + βnd2*). Biologically effective dose (BED) of palliative radiotherapy schedule 50Gy in 20 fractions comes around 62.5Gy. This comes closest to the radical radiation dose BED which is 79.2Gy.

EVIDENCE FOR HYPOFRACTIONATED PALLIATIVE RADIOTHERAPY REGIMENS

An optimal palliative radiotherapy regimen for oral cavity cancer is still in evolution. In literature, various hypofractionated regimens have been tried. Limited prospective studies, high rate of attrition in trials and poor compliance to therapy are some of the causes for paucity of literature. In a developing country like India, limited resources in terms of expertise and equipment, makes the scenario worse. This has resulted in failure of identifying an ideal subgroup of patients who benefit from palliative radiotherapy(41). The NCCN has listed various palliative radiotherapy regimes including 50Gy in 20 fractions & 30Gy in 10 fractions and advises evaluation of patients performance and treatment tolerance ,tumour response and systemic progression(42).The table below shows the various studies which have looked into the outcomes of various hypofractionated studies on palliative radiotherapy for locally advanced tumours of head and neck.

Table 6 Various Hypofractionation schedules

Author	Year	Sample	Dose in Gy	Number of fractions	Median survival (months)	Remarks
Al-mamgani et al(43)	2009	158	50	16	17m	Local Control-62% Disease-free survival-32% Overall survival-40% at one year follow-up
Lok et al(44)	2015	75	44.4	12	5.67m	IMRT was done(QUAD shot)
Stevens et al(45)	2011	55	50	20	5.7 m	Retrospective study; Few patients received other regimens like 24Gy in 3# and 30Gy in 10 #
Mohanthy et al(46)	2004	505	20	5	200days	Patients showing more than 50% objective regression (PR) at tumour and nodal sites received further RT up to 70Gy.
Porceddu SV et al(47)	2007	35	30	5# in 2 weeks	6.1m	Known as Hypotrial. Additional 6Gy boost was given for <3cms
Paliwal et al(48)	2012	50	20	5	--	Partial response in 92%
Ghoshal et al		15	14	4	---	QUAD SHOT 14Gy in 4 fractions given twice daily in two days
Chen et al	2008	12 7 5	30Gy 37.5Gy 20Gy	10 15 5	8 months 5 months 3 months	Grade III toxicity: 49%,,29%,20% respectively
Minatel et al	1997	58	50Gy	20	--	Overall treatment time : 6 weeks because 2 weeks break after 25Gy.

Almamagni et al studied 158 patients with head and neck cancers (36 of them were oral cavity cancers) with 3.125Gy per fraction for 16 fractions which was named as 'Christie scheme' as it was adopted from Christie Hospital in Manchester. The patients in this study had a median survival time was 1.5 years. Forty percent of patients survived more

than 12 months. They calculated one year and three year actuarial rates of loco-regional control, disease-free survival and overall survival which were 62%, 32% and 40% respectively at one year and 32%, 14% and 17% respectively at the end of three years .Mucositis was the most common toxicity observed which was noted in 65% of patients. Weight gain, pain relief and performance status improvement were 50%, 77% and 47% respectively for patients who survived more than a year.

Minatel et al studied 58 head and neck cancer patients (25 were oral cavity) from 1990 to 1998 with 50Gy in 20 fractions with concurrent bleomycin. Radiotherapy was delivered in split course of two. Each course consisted of 25Gy in 10 fractions for 2 weeks duration followed by a similar second course with a two weeks gap in-between. Total duration of treatment was six weeks. Bleomycin was delivered 10gm twice a week with a cumulative cut off dose of 60 mg. The rate of disease local control in this study was 69% and median symptom free duration was of 7 months .The symptom relief rate was 81%.

Stevens et al conducted a retrospective analysis of patterns of care, outcomes in148 patients who received different palliative radiotherapy regimens. In the study there were 27 oral cavity patients were present and 50Gy in 20 fractions schedule was used in 55 patients. The median survival in patients used 50Gy in 20 fractions was 5.7.months.This study noted that high dose of radiation is associated with increase in durability of locoregional control and decrease late toxicity.

In India, Ghosal et al studied on QUAD shot regimen in 15 patients in a tertiary centre .This regime delivered14 Gy in two days with two fractions per day six hours apart. Outcomes and symptomatic response was assessed using University of Washington score. Study had documented 86.7 % of patients had more than 50% improvement in objective score.

Mohanthy et al studied on 20Gy in 5 fractions in 505 patients (12.5% were oral cavity cancer patients) and median survival was reported as 6.5 months. 47%‑59% of patients had symptomatic relief for pain, difficulty in swallowing and cough. One year survival was as 30%.

In our institute during (2010-2012) 36patients with inoperable head and neck cancer who received 40 Gy in 10 fractions with 2 fractions per week. Treatment related toxicity and quality of life was assessed using Radiation Therapy Oncology Group criteria and Functional Assessment of Cancer Therapy (FACT H and N) respectively before starting and at the completion of radiotherapy. Majority of them were oral cavity cancer patients (36%).Quality of life assessment in different domains showed improvement in social well‑being domain post radiotherapy (17.4 vs. 20.01, $P = 0.03$), but no significant change was observed in head and neck specific score. Commonest presenting complaint was pain and reduction of pain was observed in 88% patients.

Treatment Response Assesment

The primary outcome of interest of all palliative radiotherapy trials are symptom relief and improvement in quality of life. Since intent of treatment is palliation of symptoms with poor median survival rates, secondary outcomes assessed in majority of the trials are locoregional control ,disease free survival and toxicity of radiotherapy (49).An objective way of measuring of palliation of symptoms for assessment in trials has always been a subject of debate . Although there are many ways to measure the frequency and severity of diseases, data on measuring the health of a patient are not robust .World Health Organization (WHO) defines health as "A state of complete physical, mental, and social well-being not merely the absence of disease"(50).And the term "Quality of Life" as per WHO is an individual's perception of their position in life taking into account of the culture and value systems in which they live and in relation to their goals, expectations, standards and concern. Various factors affect quality of life including person's physical health, psychological state, level of independence, social relationships, beliefs, interaction with surroundings etc.(50)

Oral cavity cancer and its treatment affect a variety of body functions, most notably swallowing, and speaking. This causes significant physical, emotional and social problems, reducing quality of life (QoL) in patient undergoing treatment for oral cavity malignancies. Various tools have been devised to measure quality of life in head and neck cancers. Ideal properties of a quality of life assessment tool are reliability, validity

and availability in all regional languages(51).Functional Assessment of Cancer Therapy-Head and Neck(FACT-H&N),European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, H&N35, McMaster HNRQ, University of Washington (UWQOL) are some of them(51).

In the present study we have used Cancer EORTC QLQ-C30,H &N35 and Euro QOL Group(EQ-5D-3L) health questionnaire. The EORTC QLQ-C30 is a questionnaire developed in 1986 to assess the quality of life of cancer patients in international trials. It has been translated and validated into 81 languages and is used in more than 2,000 studies all over the world(52). Several modifications have been done in the questions since it's incept. Presently QLQ-C30 Version 3.0 is the most recent version and its used in this study also(53). The QLQ-C30 consists of 30 questions which assess various aspects of quality of life..It includes five functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning) and global health status and nine symptom scales (fatigue, pain, dyspnoea, constipation, diarrhoea, nausea and vomiting etc) and a global health status and quality-of-life scale. Global health status has been graded from one to seven ranging from very poor to excellent.

Table 7 EORTC QLQ 30 scales

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

EORTC QLQ-C30 is supplemented by disease-specific modules (Head & Neck, Oesophageal, Breast, Lung etc)(25).In our study we have incorporated HN35 questionnaire which is the specific module for head and neck malignancies.HN35 has formulated thirty five multiple choice questions which has been divided into eighteen groups which will address symptoms related to head and neck malignancies and its treatment related toxicities.The patient is asked to rate the intensity of symptom as a numerical from one to four (1=not at all, 2=a little, 3=quite a bit and 4= very much) . Five questions of the H&N35 are answered with a yes or no. These include the information

regarding use of pain killers, feeding tube, nutritional supplements and weight of the patient

Table 8 EORTC QLQ HN 35 scales

Scale name	Scale	Number of items	Item range*	QLQ-H&N35 Item numbers
Symptom scales / items				
Pain	HNPA	4	3	1 – 4
Swallowing	HNSW	4	3	5 – 8
Senses problems	HNSE	2	3	13,14
Speech problems	HNSP	3	3	16,23,24
Trouble with social eating	HNSO	4	3	19 – 22
Trouble with social contact	HNSC	5	3	18,25 – 28
Less sexuality	HNSX	2	3	29,30
Teeth	HNTE	1	3	9
Opening mouth	HNOM	1	3	10
Dry mouth	HNDR	1	3	11
Sticky saliva	HNSS	1	3	12
Coughing	HNCO	1	3	15
Felt ill	HNFI	1	3	17
Pain killers	HNPK	1	1	31
Nutritional supplements	HNNU	1	1	32
Feeding tube	HNFE	1	1	33
Weight loss	HNWL	1	1	34
Weight gain	HNWG	1	1	35

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

Scores are collected from the patients for each question are grouped into a symptom scale or functional scale or global health status scale. The average of the items that contribute to a particular scale is called the raw score. Raw score is then normalized to a value between zero to hundred which will make data analysis easier. EORTC has

developed various formulae to convert raw score to a value between zero to hundred which is shown below.

For global health status $S = \{(Raw\ Score - 1)\ range\} \times 100$

For functional scale $S = \{1-(Raw\ Score - 1)\ /range\} \times 100$

For Symptom scales $S = \{(Raw\ score - 1)\ range\} \times 100$

Range is the difference between the maximum possible value and minimum possible value. After the linear transformation we will get a value between zero and hundred which may represent either functioning or intensity of symptom. Among symptom scales hundred represents the highest degree of symptom and poor quality of life. But in function scales hundred describes the best function. In the yes/no questions of EORTC H&N35 the score hundred means presence of the symptom. In short a high score for a functional scale and global health status indicates a high healthy level of functioning and a high score for the global health status respectively .But a high score for a symptom scale indicates a high incidence of symptoms or poor quality of life.

EORTC QLQ 30 and HN 35 is a validated quality of life tool. Various studies have tried to correlate EORTC questionnaires score and clinical significance. King et al and Osoba et al suggested a ten point change in score before and after intervention can be considered as clinically significant.

The EuroQol Research Foundation which is network of international multidisciplinary researchers mainly from different countries of Europe formulated an single index value

for health status in 1990 known as EQ-5D-3L(54).It's a well validated multilinguistic quality of life assessment tool.EQ-5D-3L assesses the patient's quality of life in five dimensions which include mobility, self-care, usual activities, pain, discomfort and anxiety/depression. Each dimension has 3 levels ranging from no problems to extreme problems. The patient is asked to indicate the health state by ticking in the box against the most appropriate statement in each of the 5 dimensions(55). The EQ visual analogue tool measures the patient's health status on a scale which the lies between 'Best imaginable health state' and 'Worst imaginable health state'(56). Thus EQ-5D-3L gives a quantitative measure of patient's perspective of health.

Another major issue which is encountered by patients undergoing palliative radiation therapy is the treatment related toxicities which can adversely affect quality of life. Most common acute side effects are dermatitis, mucositis, pain and dysphagia leading to need for Ryles tube insertion. Late effects of head and neck radiation like hypothyroidism has less significance in a palliative setting where overall survival is less. In our study we used Common Terminology Criteria for Adverse Events (CTCAE) published by National institute of Health provides a grading system to report these adverse event.(57).

Justification for study

As it is evident from the literature review cancer in oral cavity is very common and in India majority of these are detected at an advanced stage. Most patients will have complaints of pain, difficulty in swallowing, difficulty in opening mouth, speech problem .Many patients are unsuitable for surgery as they have advanced stage of disease or they are unfit for any intervention due to other medical problems. In these patients symptoms can be relived to an extent by palliative radiotherapy. In this study we assessed the symptoms of the patient before treatment and after treatment and assessed how much improvement in symptoms has been achieved with systematic documentation of the symptom relief using validated QOL questionnaires. There are limited studies for evaluating the symptom relief after this palliative radio therapy regimen using well established quality of life tools. Most studies on Palliative RT in Head & Neck Cancers have a heterogeneous mix of patients belonging to the various Head & Neck cancer sub sites, making it difficult to draw meaningful conclusions while treating patients in our clinics. By quantifying the symptomatic relief by this palliative radiation therapy regime & stringent recording of QOL, we can appropriately select patients in our clinic with inoperable oral cavity cancers, who will benefit from this regime.

Methodology

MATERIAL AND METHODS:

a. Setting

Patients with locally advanced oral cavity malignancy with squamous cell carcinoma histology attending the outpatient clinic of Radiotherapy Unit 1,Surgery Unit 1 or Palliative Care Unit were discussed in the Head & Neck Multidisciplinary Team meeting which was held on Monday afternoons. Patients in whom the recommendation was palliative radiotherapy and fulfilling the inclusion criteria were enrolled in the study after an informed consent (The consent form along with the Patient Information Sheet is attached in Appendix 1).

No specific sampling strategy was employed to enroll the patients. The baseline data was entered into a numbered proforma.

INCLUSION CRITERIA

1. Surgically unresectable oral cavity malignancies (squamous cell carcinoma) with clinical involvement of infratemporal fossa involvement, hard and fixed N3 nodes or extensive skin involvement with or without cutaneous nodules or severe trismus

2. Stage IVA,IVB disease-poor performance status, significant comorbid illness

3. Stage IVC disease-for palliation of local symptoms

EXCLUSION CRITERIA

1. Previous history of head and neck malignancy treated with radiotherapy
2. Age less than 18

STUDY DESIGN:

STUDY TYPE: Prospective Observational Study

Date of commencement of the study: January 2015

Date of last enrolment: August 2016

Sampling and consent:

The sample size was calculated using nMaster 2.0 software.

With reference to the article published in the International Journal of Radiation Oncology, Biology and Physics in November 15, 2011 Volume 81, Issue 4, Pages 958–963 (Retrospective Study of Palliative Radiotherapy in Newly Diagnosed Head and Neck Carcinoma: Christian M. Stevens et al) the sample size was calculated using nMaster 2.0 software as follows :

As per the reference article mean duration of symptom free was taken as 3 months which ranges from 1-7 months. The sample size for this study was decided according to following formula and calculations.

Table 3 Calculation of sample size

Single Mean - Estimating the population mean - Absolute precision				
Standard Deviation	1.5	1	1.5	1
Absolute Precision	1	0.5	0.5	0.25
Desired confidence level (%)	95	95	95	95
Required sample size	9	15	35	61

Formula

$$n = \frac{z^2_{1-\alpha/2}\sigma^2}{d^2}$$

Where,

σ : Standard deviation

d : Precision

1- α/2 : Desired Confidence level

Institutional review board approval and funding

Institutional Review Board (IRB) approval was obtained prior to the commencement of the study (IRB No.9257)

Detailed diagrammatic Algorithm of the study

Biopsy proven locally advanced inoperable Squamous Cell Carcinoma of the oral cavity whose treatment intent is palliation as decided by the Head & Neck Multi-Disciplinary Team

a. Clinical involvement of infra temporal fossa
b. Hard and fixed N3 nodes
c. Extensive skin involvement with or without cutaneous nodules
d. Severe trismus
e. Stage IVA,IVB disease-poor performance status, significant comorbid illness
f. Stage IVC disease-for palliation of local symptoms

Initial patient assessment of patients' symptoms and quality of life was done before starting treatment with the EORTC QLQ-C30 & EORTC QLQ - H&N35&EuroQol.

Patient answered the questionnaire on their own before treatment.

Initiation of radiotherapy with 50 Gy in 20 fractions,2.5-Gy per fraction daily with five fractions per week for a total duration of 4 weeks

As per institution protocol of weekly assessment of patients undergoing radiotherapy, toxicity was graded using CTCAEv4.0 head and neck.

Quality of life and symptom relief assessment was done on completion of treatment after 4 week

In first follow up after 6 weeks patient was assessed for symptomatic relief and improvement in quality of life using EORTC QLQ-C30 & EORTC QLQ - H&N35 tool& Euro Qol tool.

Median scores of the individual domains before, after radiation and in the first follow up with this radiation schedule of 50Gy in 20 fractions were assessed.

Patient workup and treatment

Patients who fulfilled the inclusion criteria were enrolled in the study after getting an informed consent and underwent the following steps in sequence; detailed history taking followed by thorough general, systemic and local examination and investigations. All findings were documented in a numbered proforma. Before starting treatment assessment of patient's symptoms and quality of life was done with the EORTC QLQ-C30 & EORTC QLQ - H&N35 & Euro QoL.

Radiation therapy planning and treatment delivery included the following steps in sequence

1. Positioning and Immobilisation

2. Simulation and Field placement

3. Dose prescription and Treatment Planning techniques

4. Plan Finalisation

4. Treatment Delivery

Positioning and Immobilisation: Patient was positioned supine with arms by the side and was immobilized using a thermoplastic mask.

Simulation: Patient was simulated with the help of an Isocentric Mounted Simulator in supine position.Marking of surgical scar and enlarged lymph nodes with lead wires before obtaining a simulation film was done. Field borders were determined taking into consideration of extent of tumour and nodes.

Dose Prescription and Planning: All patients were planned for 50Gy in 20 Fractions with 2.5Gy per fraction with one fraction per day (five fractions per week) lasting for four weeks**.**The technique used is parallel opposed lateral technique.After a tumour dose of 40 Gy, the posterior margin of lateral portal is brought anteriorly to the midportion of the vertebral bodies to spare the spinal cord.

Field size, treatment distance, beam energy, beam direction, weighting, beam modification devices used during each treatment session are calculated and provided to technologists for treatment delivery. Treatment was delivered in Cobalt 60 machine (Theratron -780 or Equninox) or Linear Accelerator (Siemens PRIMUS) machine.

All patients' undergoing therapy used normal saline and thymol glycerine mouthwash, vitamin supplementation and adequate analgesics .Proper oral and skin care and diet advice were given prior to starting radiation therapy. Every patient undergoing therapy was monitored weekly in Radiotherapy on treatment checkup clinic and their nutritional status, toxicity profile according to Common Toxicity criteria and tumor response were assessed, documented and decision regarding any intervention were made. Palliative care physicians and dietician's opinion were sought for issues regarding pain management and nutrition respectively. On completion of therapy quality of life was reassessed with the EORTC QLQ-C30 & EORTC QLQ - H&N35 & Euro QoL.

Follow-up

First follow up was done after six weeks and patients were assessed for symptomatic relief and improvement in quality of life and tumor response is assessed clinically or radiologically if indicated. Based on the patient performance status and tumor response further intervention like oral biological or palliative chemotherapy were planned on a case to case basis.

Statistical Analysis

The data was entered and analysed using SPSS 17.0 software. The mean, median and SD was used to represent the outcome variables such as Quality of Life and symptom free time etc. We tested the data this using the Non parametric test for the related samples (Friedman's test) for testing the significance difference in QOL before and after treatment.

Results

Seventeen eligible consecutive patients were enrolled in this prospective study after getting informed consent. Patient characteristics and treatment details are presented in Table 10 & 11

Table 4 Demographics (n=17)

Age (years)		
Median		54 (35-71)
Gender		**Frequency (%)**
Male		14(82)
Female		3(18)
Histology		
Squamous cell carcinoma		17(100)
RISK FACTORS		
Alcohol		3(18)
Tobacco		12(71)
	Smoking	2
	Smokeless	4
	Both	6
Site		
Tongue		9(53)
Floor of mouth		1(6)
Buccal mucosa		5(29)
Retromolar trigone		1(6)
Submandibular gland		1(6)
TNM		
T4		17(100)
N0		5(29)
N1		2(12)
N2		8(47)
N3		2(12)
M0		17(100)
STAGE AT DIAGNOSIS		
III		0(0)
IV A		12(71)
IVB		5(29)

Most common presenting complaint was non healing ulcer which was noticed in 15 patients (88%) followed by neck swelling (12%).

Table 5 Treatment characteristics

TECHNIQUE	
Parallel opposed Lateral	17
Perpendicular wedge	0
Machine	
Cobalt 60	16
Linear Accelarator	1
Completed RT	13
Breaks during RT	5
Median overall treatment time	27 days
Concurrent chemotherapy	0
Morphine	8
NG feeding during RT	6
Admissions	6
GCSF for mucositis	3

Assessment during and end of radiotherapy

Out of 17 Patients 13 completed 50Gy in 20 fractions. Two of them discontinued due to personal reasons .In two patients number of fractions were cut short to 14 fractions and 16 fractions due to radiation induced Mucositis and poor tolerance. Median RT duration was 27days (Inter quartile range 27-28days).Maximum duration was 35 days. Twelve patients completed radiation within 4 weeks. Five patients had break during radiotherapy. Grade 3 radiation induced mucositis was the most common cause of break in radiotherapy. Four patients had break in radiotherapy during third week of treatment and one patient had a break in the first week of treatment. Six patients required inpatient admission during radiotherapy for radiation induced mucositis management and pain control. Ten patient developed candidiasis during treatment which was treated with Fluconazole.

Table 6 Response assessment

Clinical response at end of RT	***END RT ASSESSMENT***	***FIRST FOLLOWUP***
Complete response	Nil	Nil
Partial response	17	8
Stable Disease	Nil	3
Progressive disease	Nil	3

Table 7 CTCAE grading of toxicities

Grade	WK 1	WK2	WK3	WK4	WK5	FIRST FOLLOWUP
Dermatitis						
3	1	1	4	Nil	Nil	Nil
4	Nil	NIL	Nil	Nil	Nil	Nil
Mucositis						
1	Nil	2	3	Nil	Nil	Nil
2	Nil	Nil	6	10	Nil	Nil
3	1	1	4	Nil	Nil	Nil
4	Nil	Nil	Nil	Nil	Nil	Nil
Dysphagia						
1	Nil	Nil	2	Nil	Nil	2
2	Nil	Nil	8	7	Nil	2
3	Nil	Nil	Nil	Nil	Nil	Nil
4	Nil	Nil	Nil	Nil	Nil	Nil
Xerostomia						
1	Nil	Nil	Nil	Nil	Nil	7
2	Nil	Nil	Nil	Nil	Nil	1
3	Nil	Nil	Nil	Nil	Nil	Nil

Assessment during follow-up .

In three patients follow up data was not available as one expired due to medical comorbidites and two of them were lost to follow up. During the first follow up (at 6-8 weeks), eight patients (57%) had partial response and three patients (21.5%) had stable disease while three (21.5%) had progressive disease. Three patients who had disease progression were started on palliative chemotherapy as they had good performance status.

Last follow up details were collected telephonically. The follow-up duration ranged from 2.3 months to 18 months with a median follow up of 8.7 months. At the end of the study period, ten patients were alive and symptomatically improved and two patients had survival more than 12 months. No patient developed a second primary during follow up.

COMPARISON OF QUALITY OF LIFE DURING RT AND FOLLOWUP

Table 8 Descriptive analysis of EORTC QOL-30 domains change over time (N=17).

Domain	Mean(SD)			MEDIAN(IQR)			
	PRE	POST	FF	PRE	POST	FF	P value
GHS	22.5(19.7)	37.7(23.2)	45.8(16.9)	20.8(15-37)	50.0(29-58)	45.8(31-58)	0.001
PF	33.7(18.6)	34.9(17)	47.1(17.0)	40.0(30-53)	40.0(32-53)	40.0(33-62)	0.150
RF	30.4(23.7)	39.2(14.4)	50.0(11.3)	33.3(25-50)	33.3(33-50)	50.0(46-54)	0.050
EF	21.6(19.1)	43.6(14.9)	44.6(18.9)	33.3(6-33)	45.8(33-60)	41.6(31-67)	0.009
CF	27.4(14.4)	38.2(12.9)	42.9(10.7)	33.3(17-33)	33.3(33-50)	41.7(33-50)	0.017
SF	20.6(16.2)	31.3(13)	38.1(18.9)	33.3(17-33)	33.3(29-33)	33.3(29-50)	0.016

[a]Friedman test

PF : Physical functioning
RF : Role functioning
EF :Emotional Functioning
CF :Cognitive Functioning
SF : Social functioning
GHS : Global quality of life

Table 9 Descriptive analysis of EORTC QLQ-30 Symptom scales change over time (N=17)

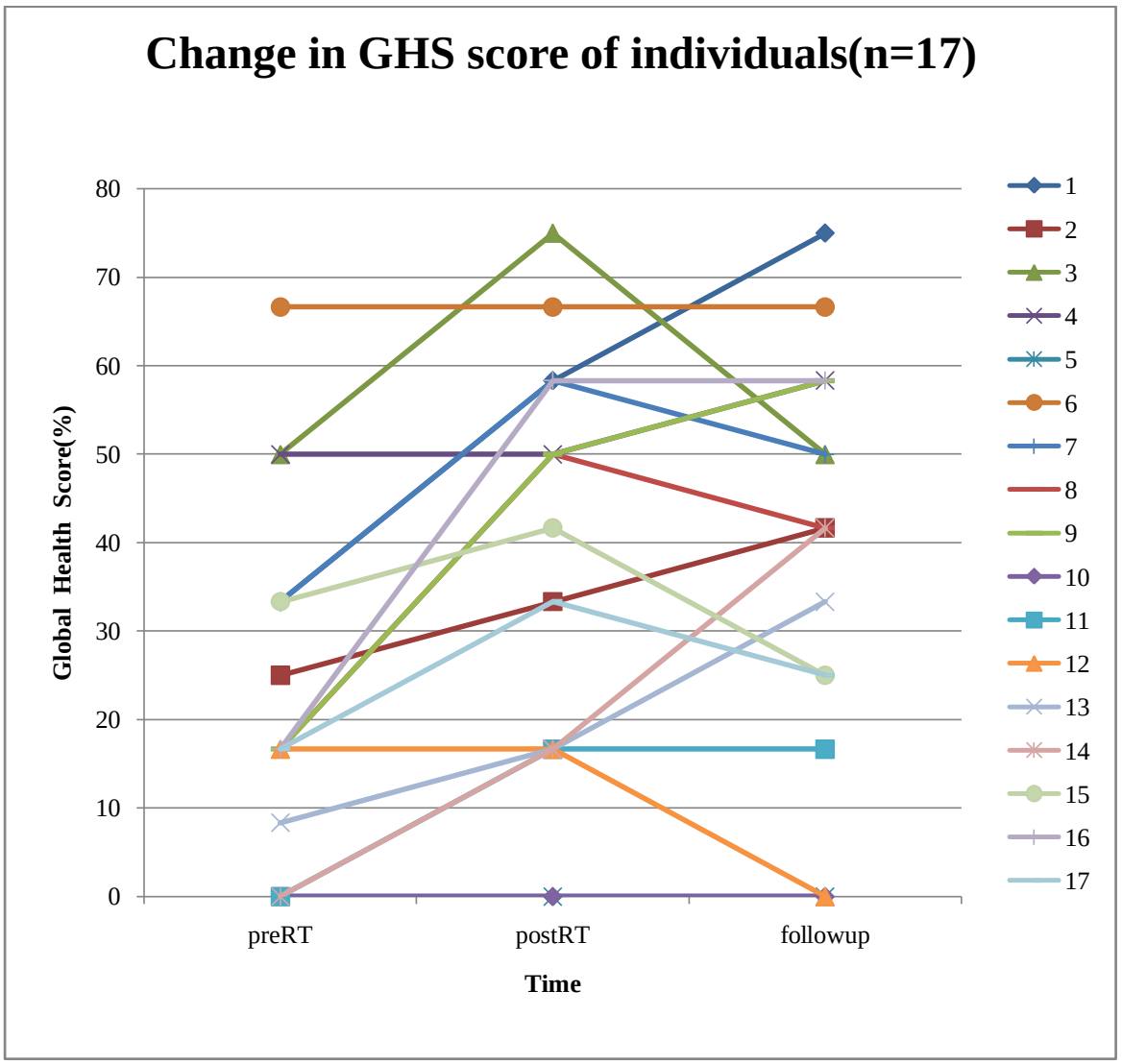
Domain	Mean(SD)			MEDIAN(IQR)			
	PRE	POST	FF	PRE	POST	FF	P value
Fatigue	73.9(18.4)	77.7(15.7)	61.9(16.7)	72.2 (56-81)	77.7(56-89)	55.6(53-78)	0.005
Vomiting	59.8(20.4)	64.7(14.3)	28.6(15.2)	58 (46-67)	67 (50-83)	17 (17-50)	0.00
Pain	90.2(15.6)	85.3(14.3)	70.2(22.8)	100 (67-100)	83.3(67-100)	75.0(50-83)	.007
Dyspnoea	1.97(8)	0(0)	4.8(12.1)	0(0)	0(0)	0(0)	.368
Insomia	56.9(25.7)	58.9(25.1)	69.0(24.3)	50(33-67)	66.7(33-75)	66.7(58-100)	.030
Appetite loss	66.7(28.8)	72.5(27.0)	76.2(20.3)	66.7(33-100)	83.3(67-100)	66.7(67-100)	.402
Constipation	17.6(26.6)	72.5(31.7)	80.9(21.5)	0(0-33)	66.7(33-100)	83(67-100)	.000
Diarrhoea	2.0(8.0)	4.0(16.2)	2.4(8.9)	0(0)	0(0)	0(0)	.867
Financial Difficulty	78.4(31.0)	80.4(20.6)	92.9(14.1)	100(33-100)	66.7(67-100)	100(92-100)	.087

Table 10 Descriptive analysis of Symptom scales QLQ-H&N35 change over time (N=17)

Domain	Mean(SD)			MEDIAN(IQR)			
	PRE	POST	FF	PRE	POST	FF	P value
Pain	83.8(14.5)	66.2(11.2)	55.4(11.1)	87.5(67-91)	62.5(56-75)	58.3(50-67)	.00
Swallowing	64.2(13.7)	49.0(25.1)	45.2(18.4)	66.6(56-75)	54.2(25-69)	45.8(31-67)	.013
Sense Problem	66.7(20.4)	56.9(22.9)	57.1(16.9)	66.6(46-71)	66.6(33-67)	50(50-67)	.159
Speech Problem	59.5(21.8)	51.0(18.0)	54.7(17.6)	66.6(39-78)	55.6(39-67)	50.0(42-67)	.010
Social Eating	63.7(16.9)	56(15.8)	52.3(17.1)	62.5(58-77)	62.5(44-67)	58.3(38-67)	.502
Trouble in social contact	67.8(9.7)	55.2(10.7)	53.3(11.1)	66.7(60-73)	56.7(45-67)	56.7(40-60)	.000
Teeth	64.7(24.9)	49(26.6)	52.4(21.5)	66.7(33-67)	50(33-67)	50(33-67)	.125
Opening mouth	82.4(17.1)	37.3(20.0)	38.1(12.1)	66.7(67-100)	33.3(33-42)	33.3(33-33)	.000
Dry Mouth	31.3(31.3)	66.7(11.8)	76.2(24.2)	33.3(0-42)	66.7(67-67)	66.7(67-100)	.000
Sticky Saliva	70.6(30.9)	55.0(26.2)	26.2(23.3)	66.7(67-100)	66.7(33-67)	33.3(0-33)	.001
Coughing	68.6(18.5)	47.0(16.9)	64.3(27.6)	66.7(67-67)	33.3(33-67)	66.7(33-100)	.022

* Higher scores on the symptom scales indicate poor status and more problems.

Change of QOL over time



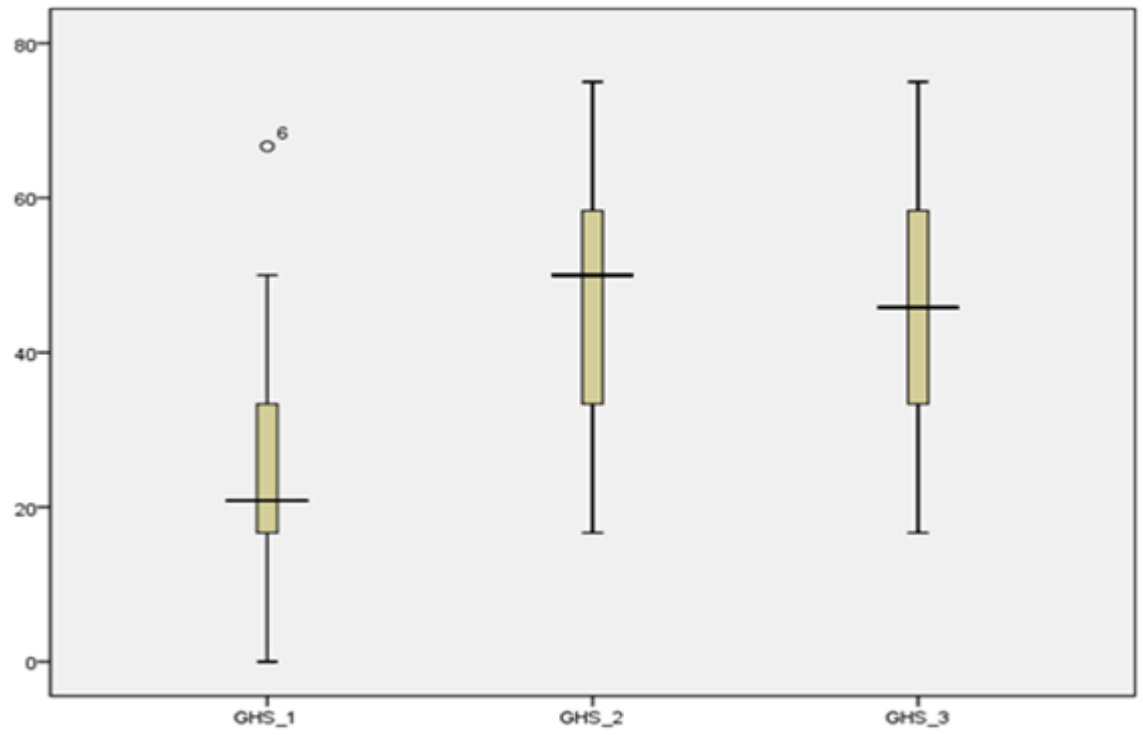
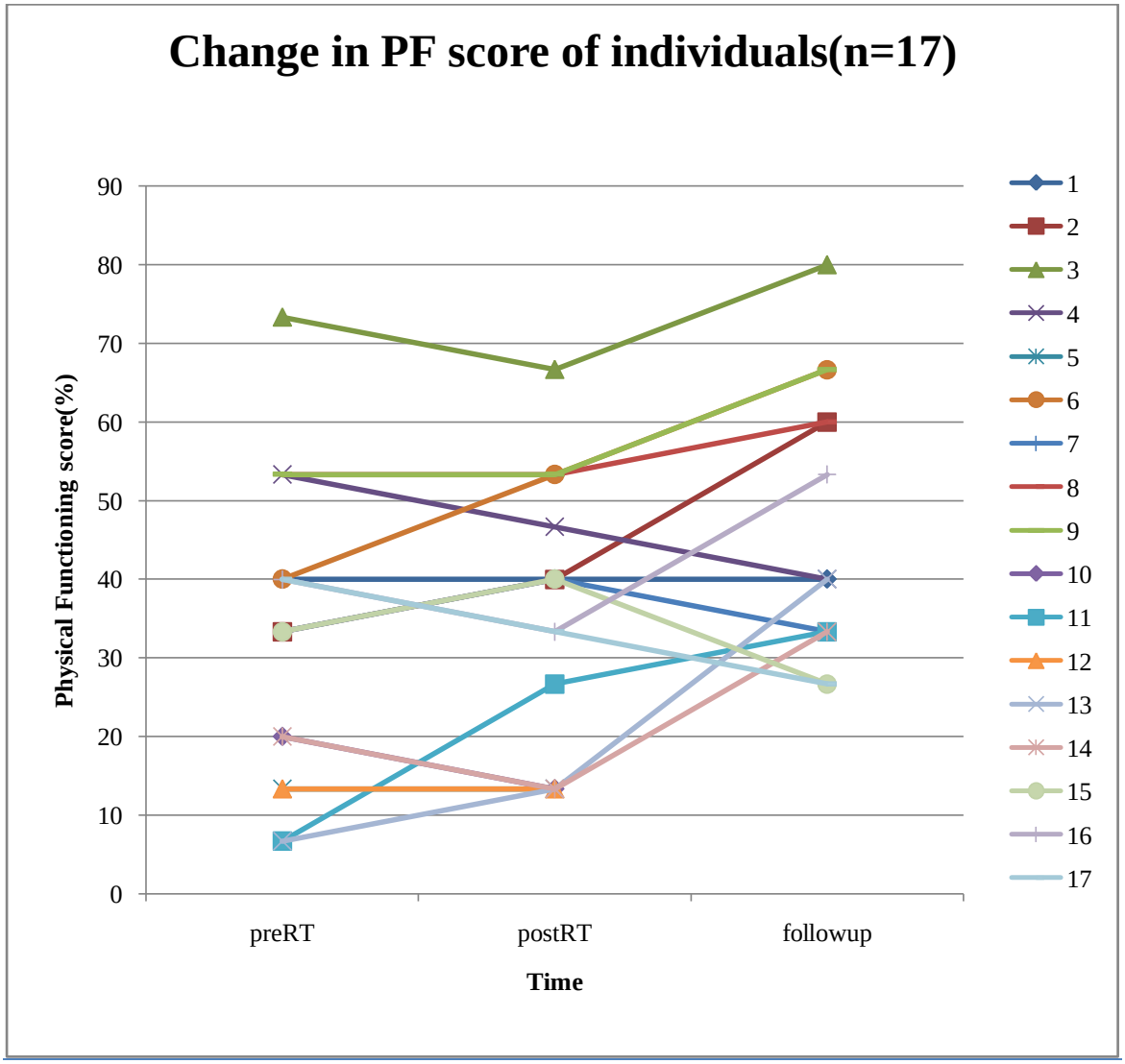


Fig 16: Box plot showing the variation in Global Health score (GHS) from preRT (GHS_1) to postRT (GHS_2) and in first follow up (GHS_3)


Change in PF score of individuals(n=17)
Physical Functioning score(%)
90
80
70
60
50
40
30
20
10
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

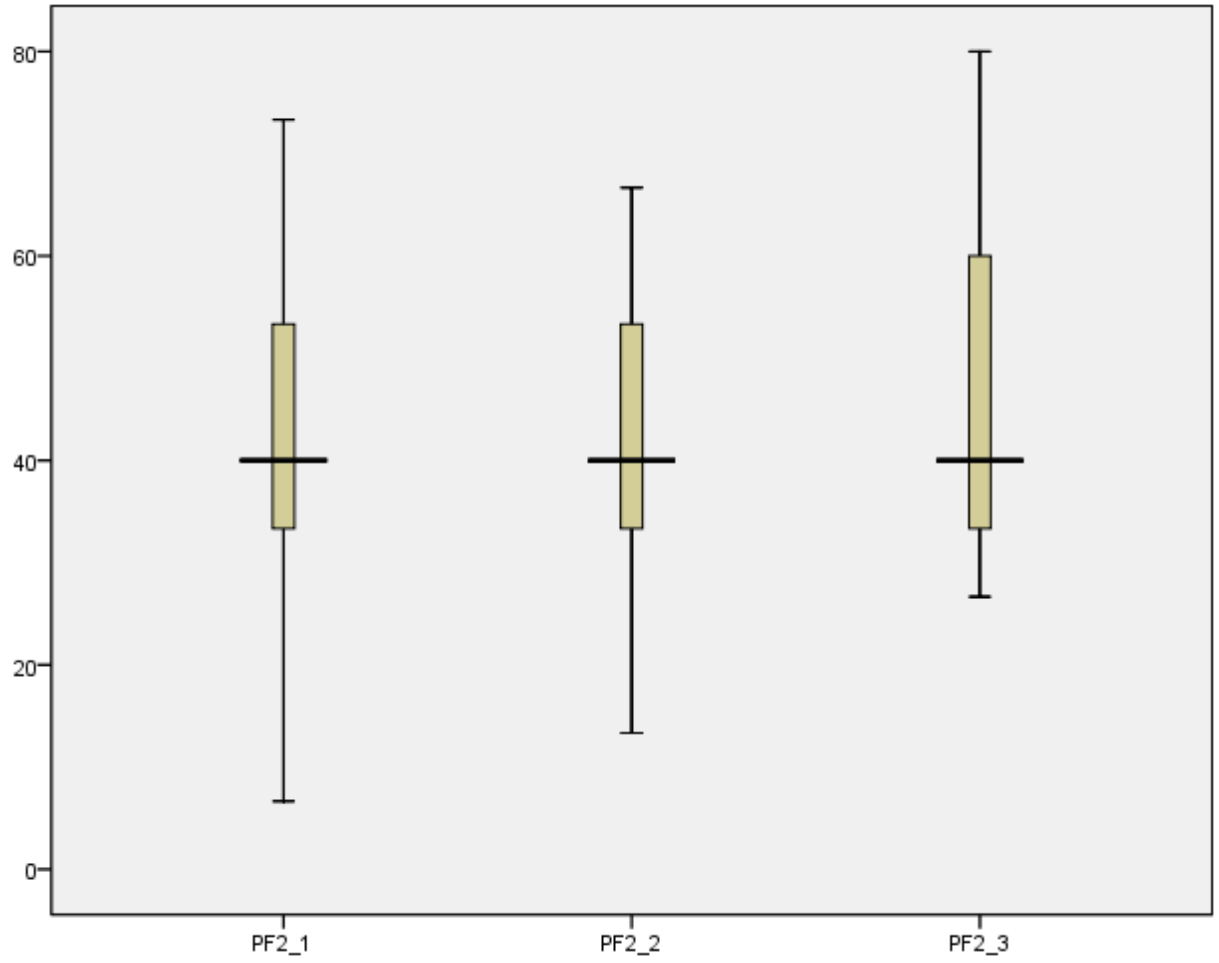
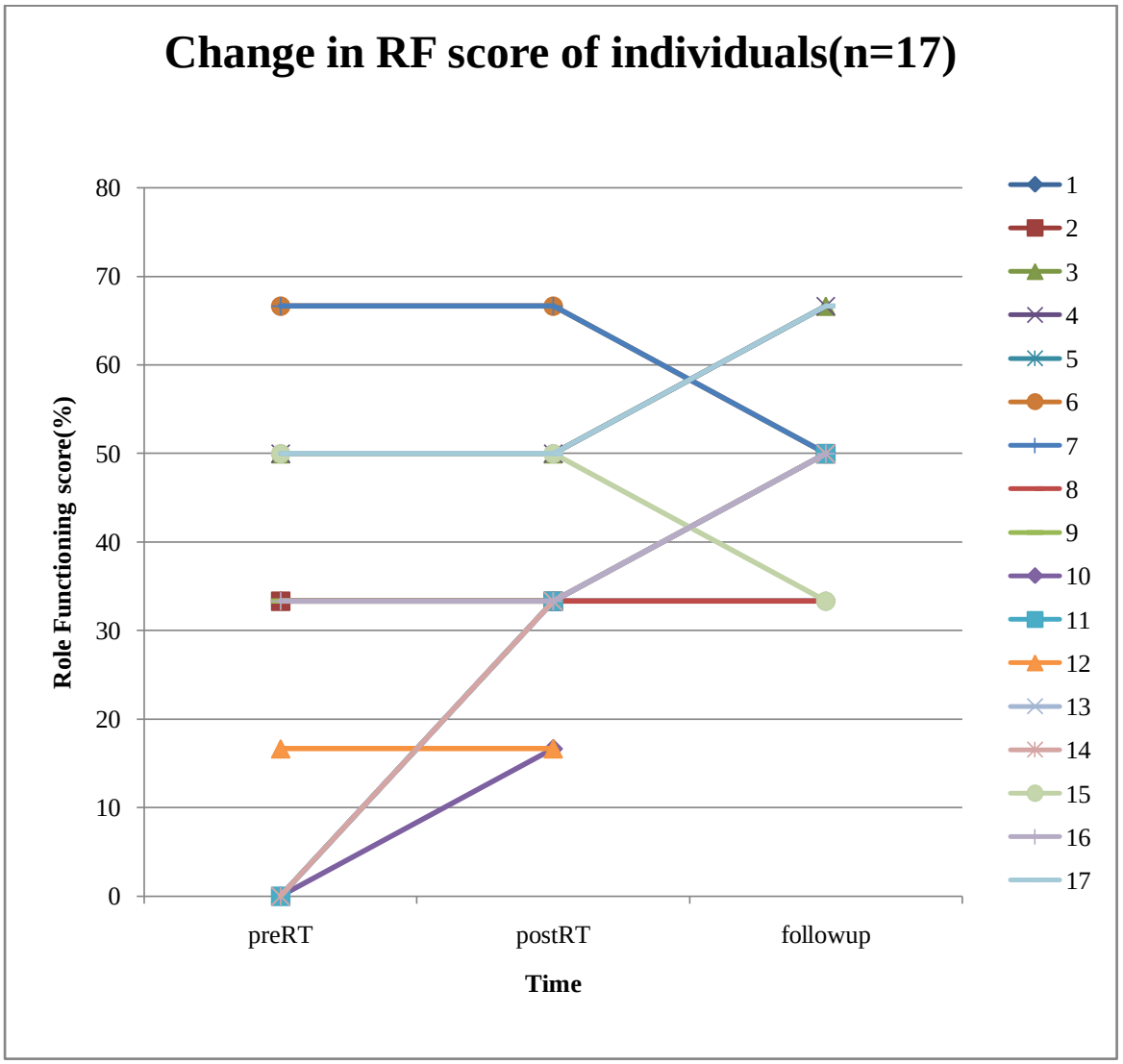


Fig 17: Box plot showing the variation in Physical functioning score (PF2) from preRT (PF2_1) to postRT (PF2_2) and in first follow up (PF3_3)


Change in RF score of individuals(n=17)
Role Functioning score(%)
80
70
60
50
40
30
20
10
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

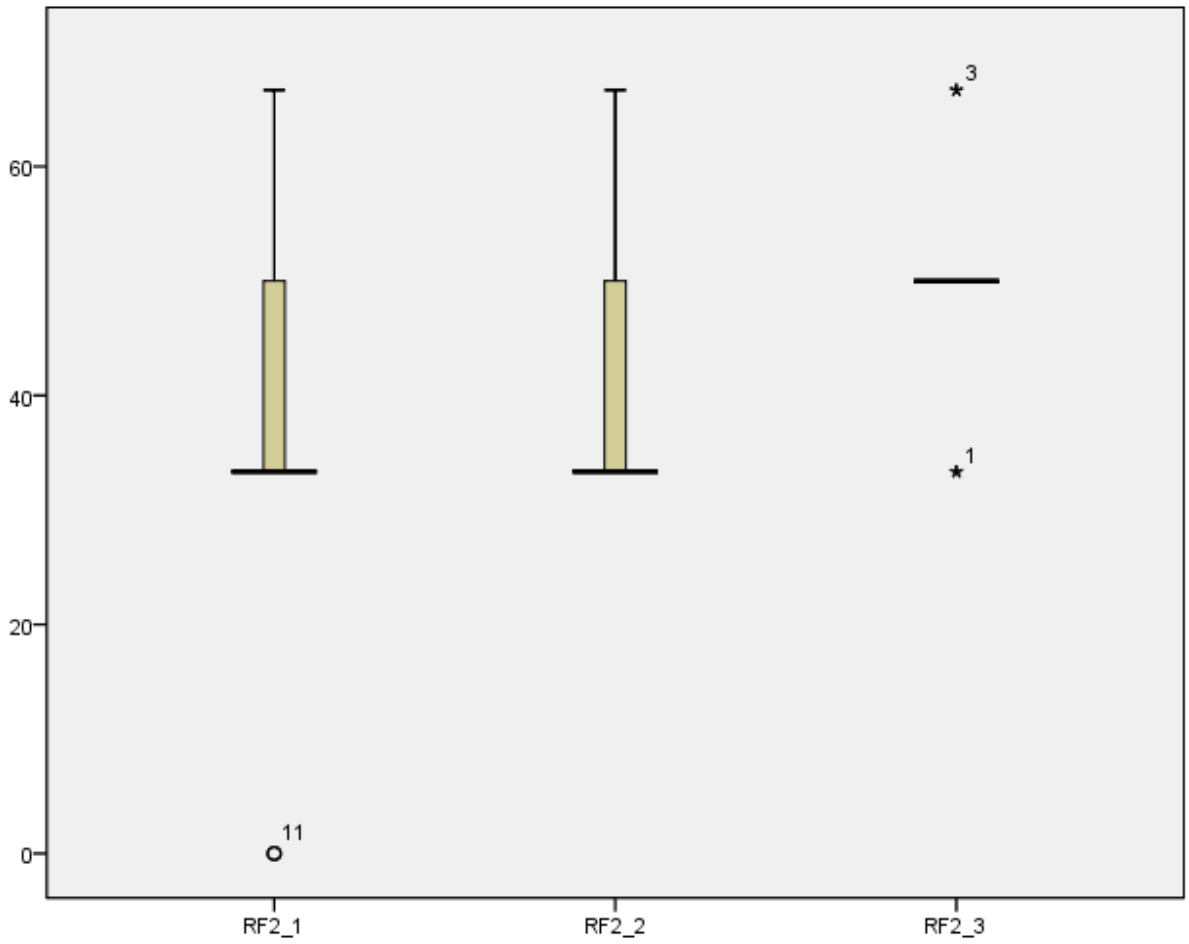
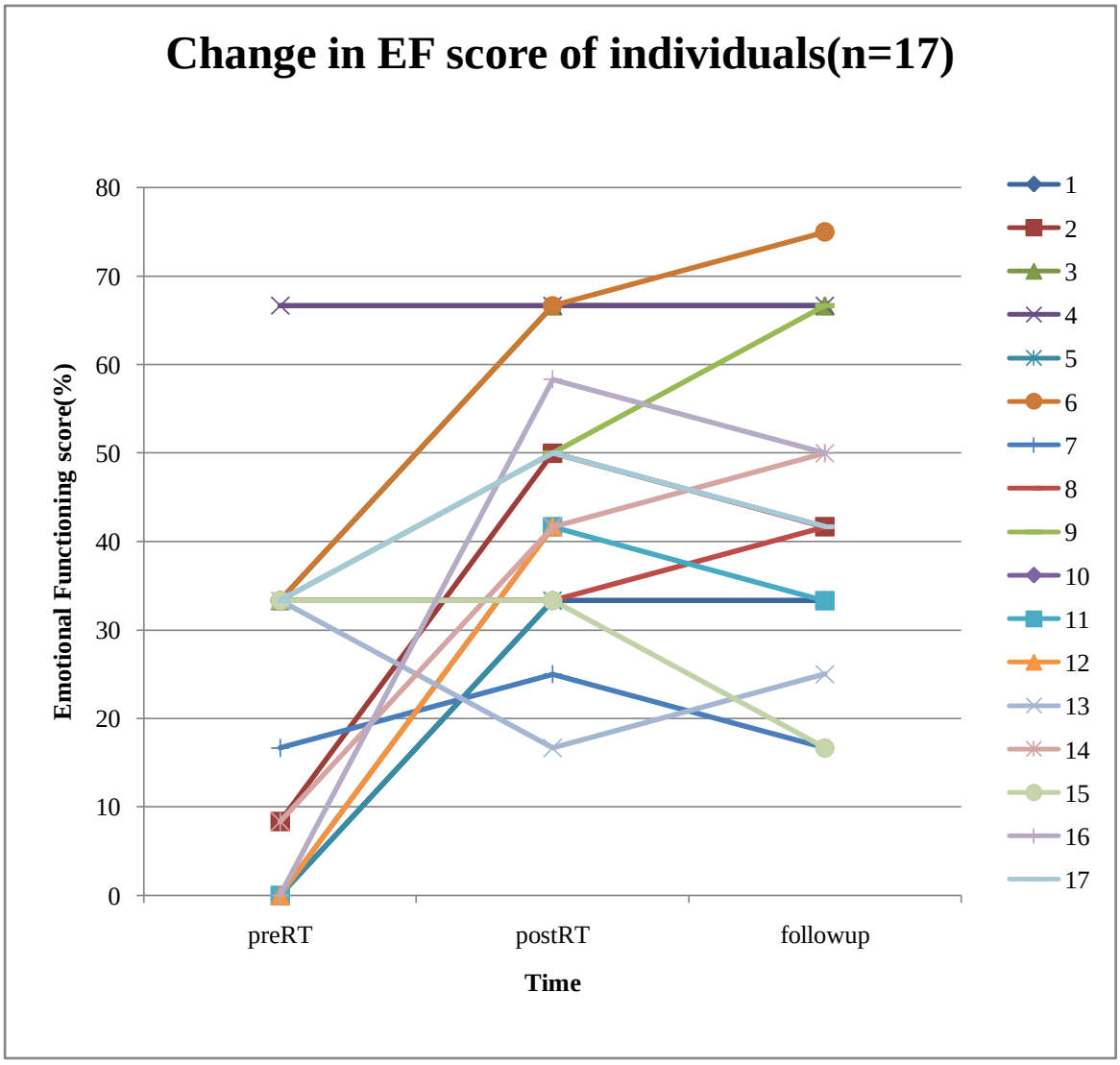


Fig 18:Box plot showing the variation in Role functioning score (RF2) from preRT (RF2_1) to postRT (RF2_2) and in first follow up (RF3_3)


Change in EF score of individuals(n=17)
Emotional Functioning score(%)
80
70
60
50
40
30
20
10
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

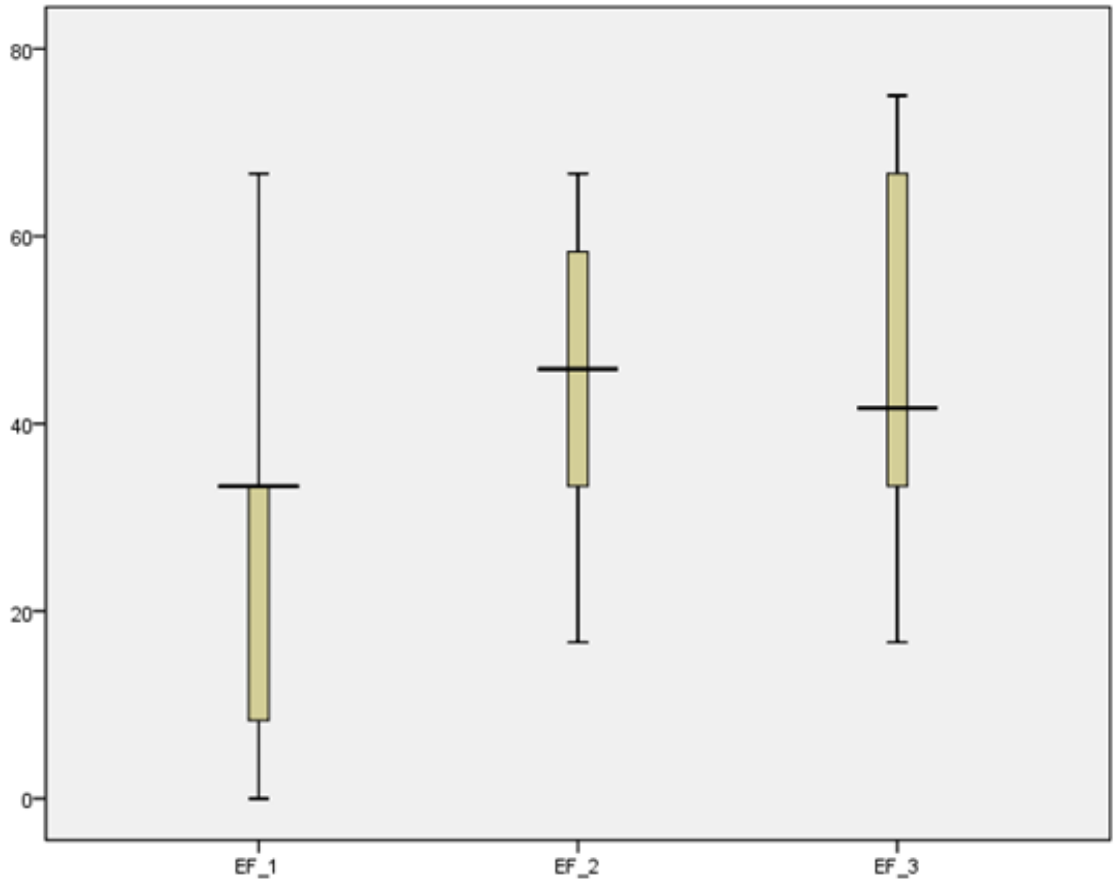
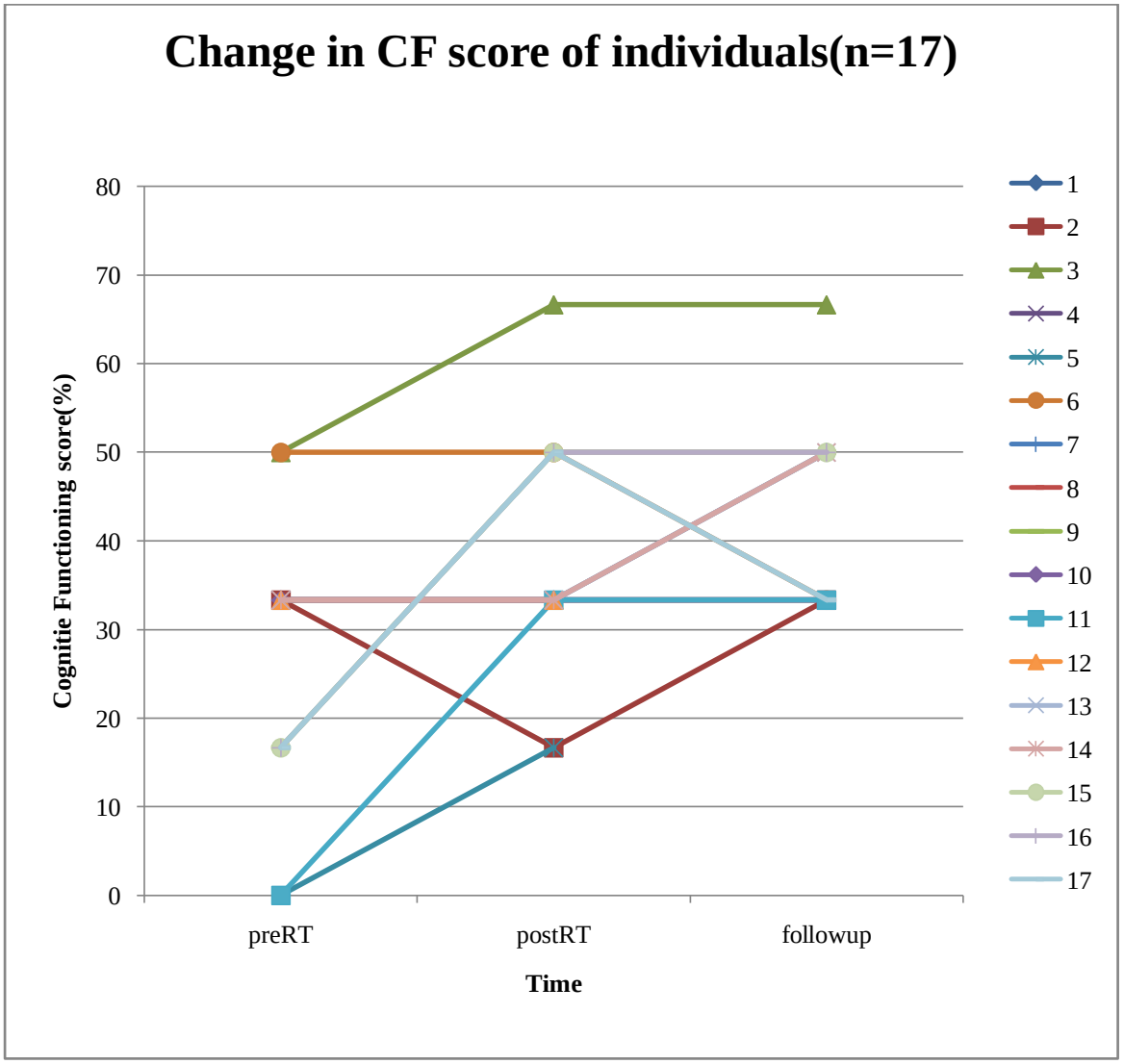


Fig 19: Box plot showing the variation in Emotional functioning score (EF) from preRT (EF_1) to postRT (EF_2) and in first follow up (EF_3)


Change in CF score of individuals(n=17)
Cognitie Functioning score(%)
80
70
60
50
40
30
20
10
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

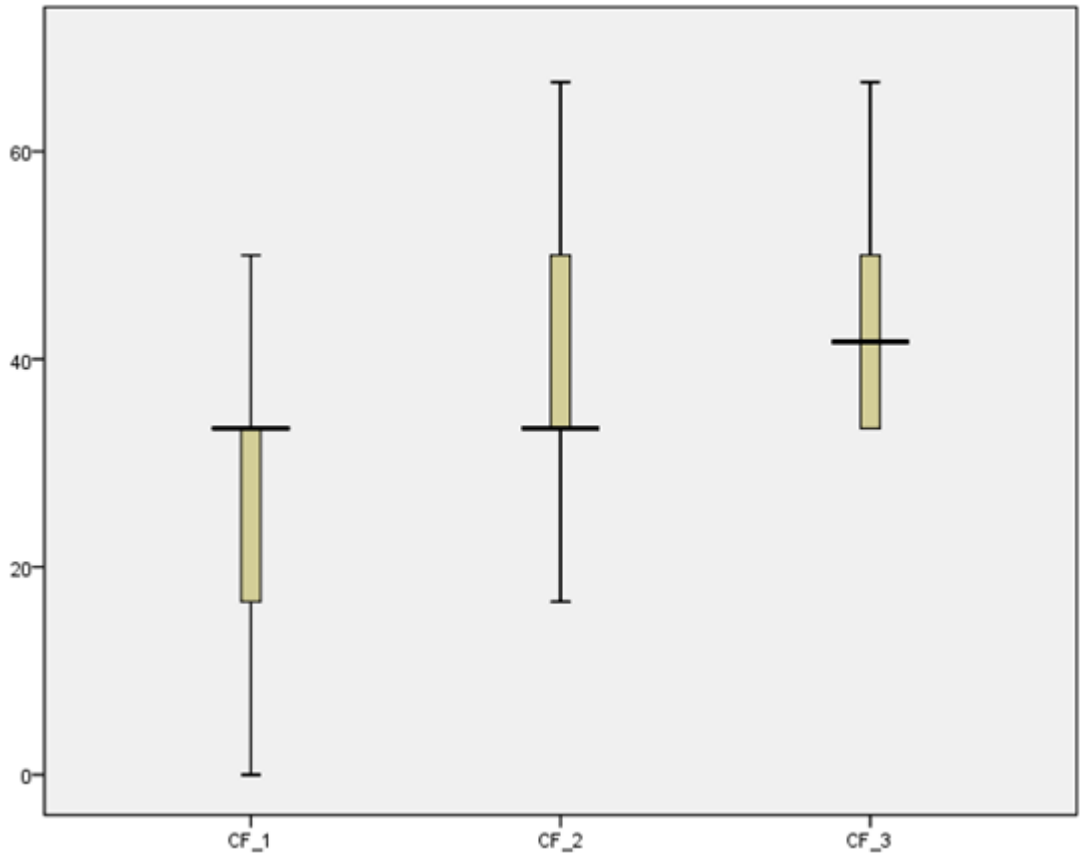
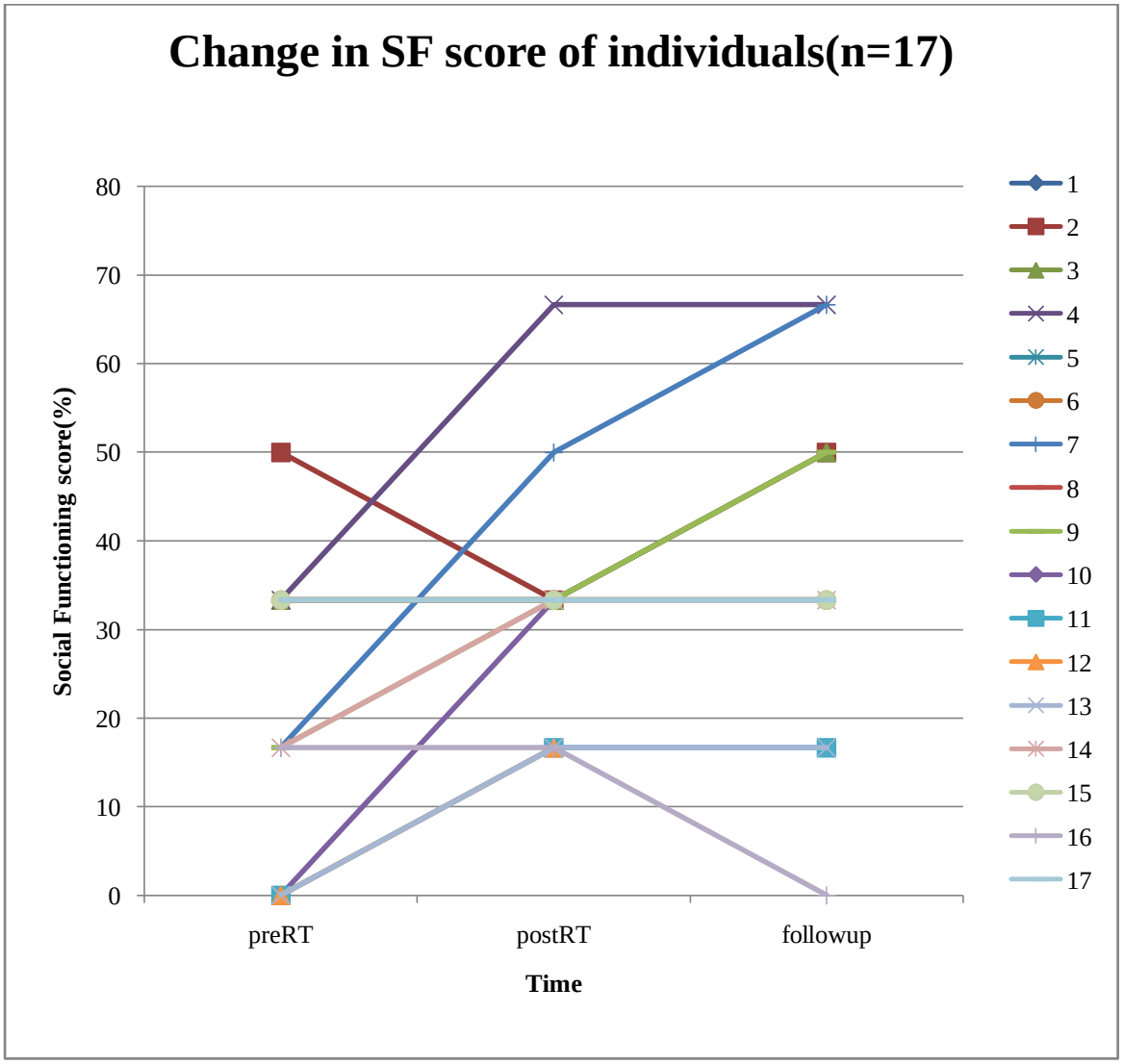


Fig 20: Box plot showing the variation in Cognitive functioning (CF) from preRT (CF_1) to postRT (CF_2) and in first follow up (CF_3)


Change in SF score of individuals(n=17)
Social Functioning score(%)
80
70
60
50
40
30
20
10
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

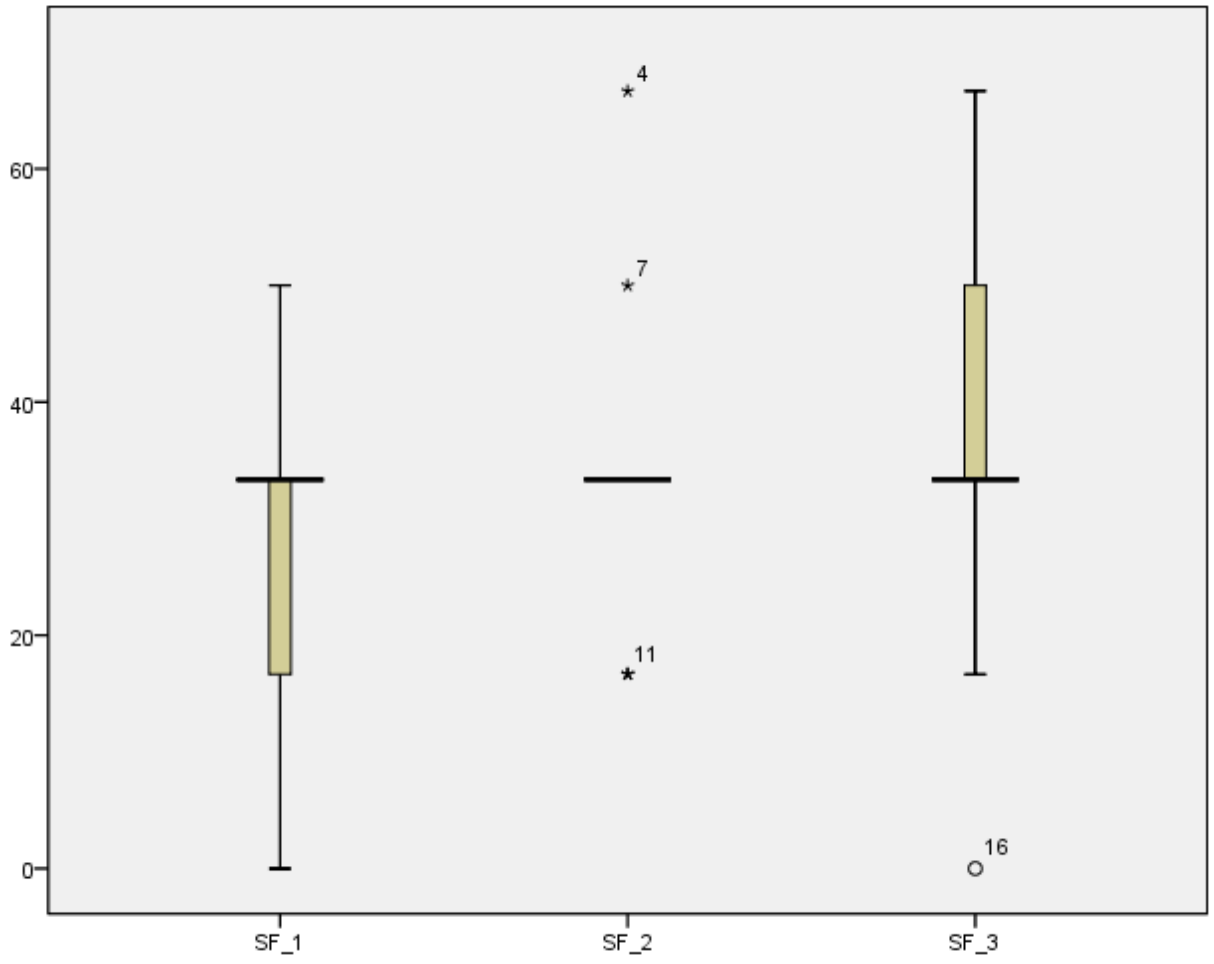
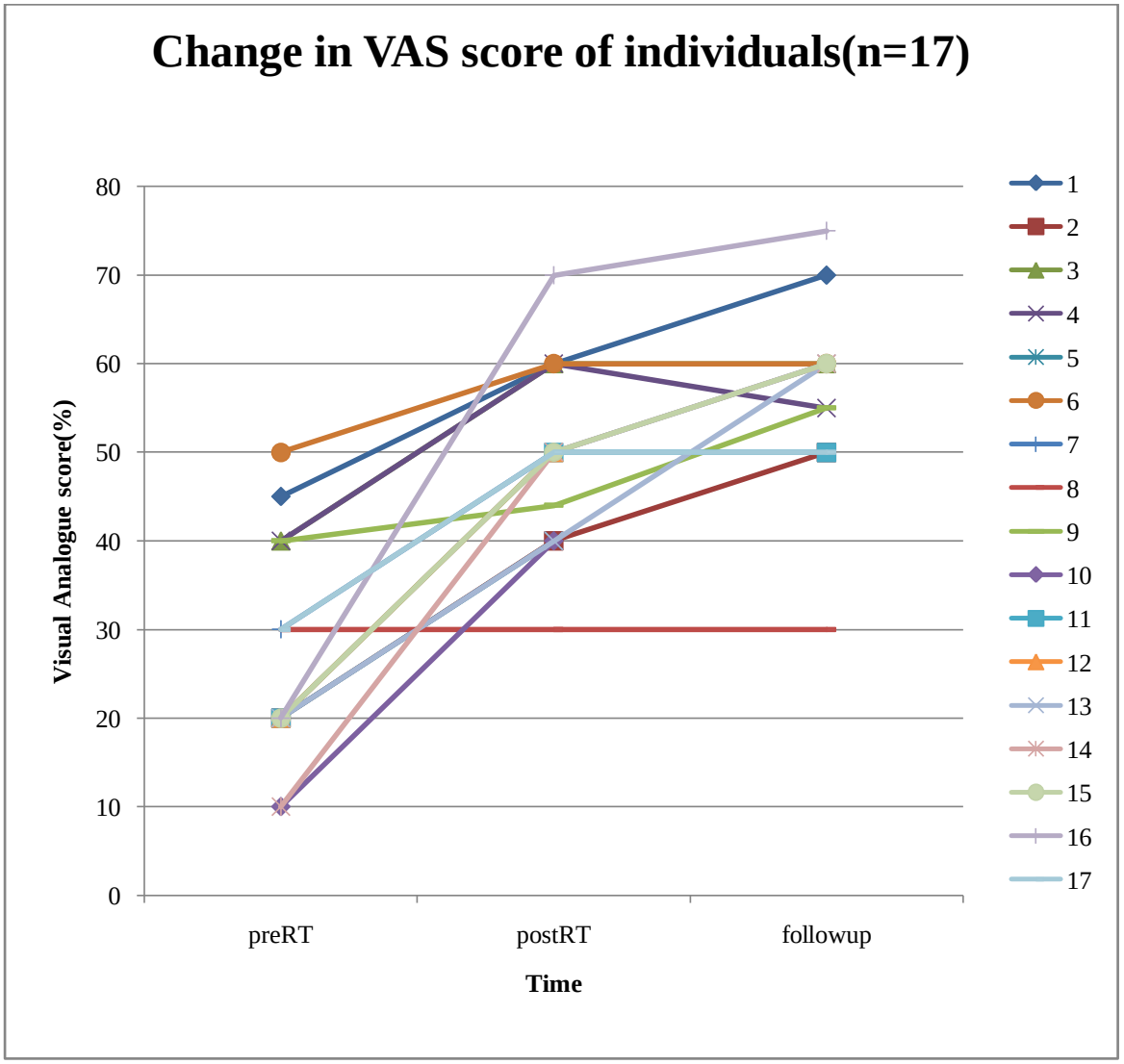
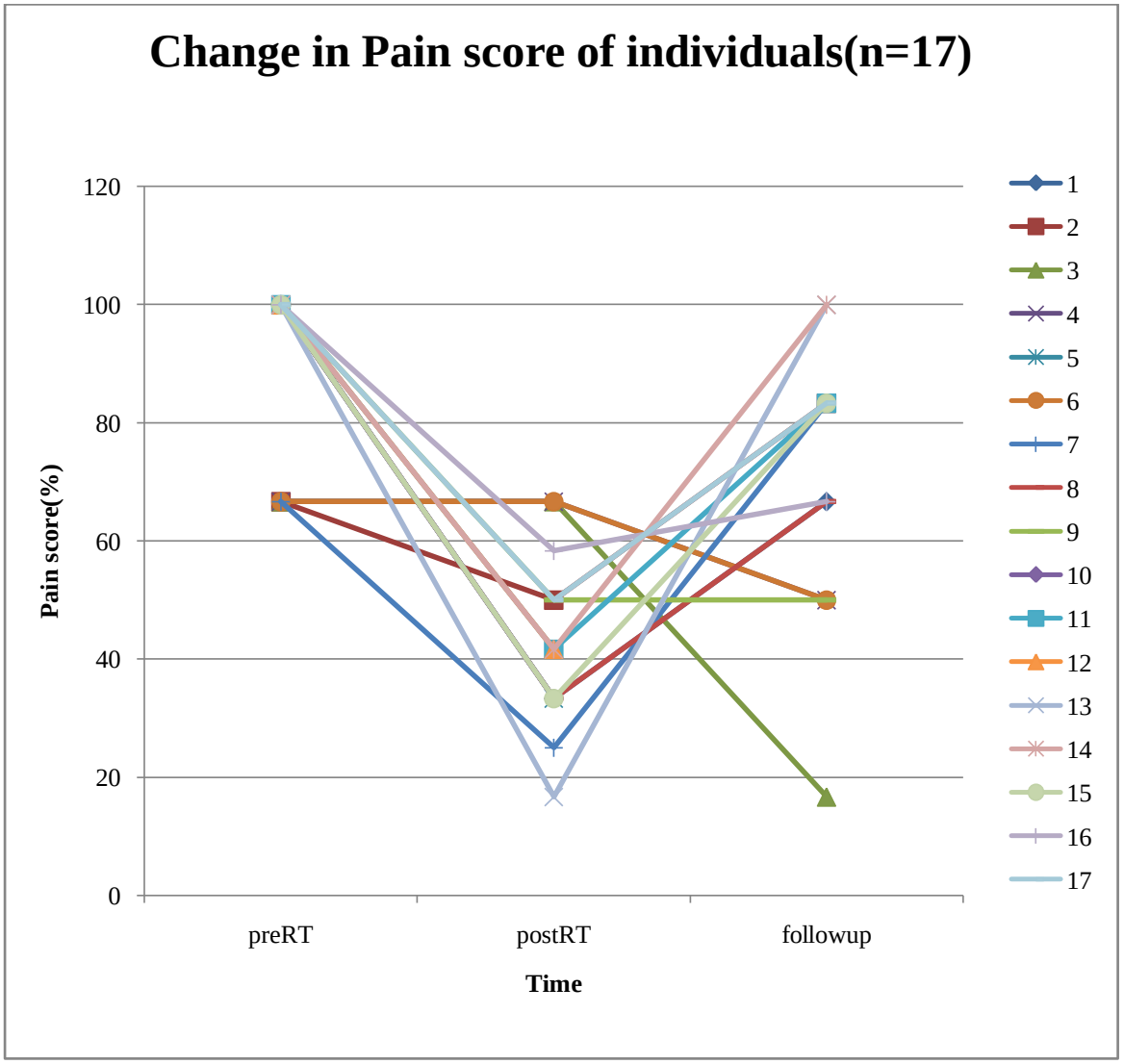


Fig 21: Box plot showing the variation in Social functioning score (SF) from preRT (SF_1) to postRT (SF_2) and in first follow up (SF_3)


Change in VAS score of individuals(n=17)
Visual Analogue score(%)
80
70
60
50
40
30
20
10
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17


Change in Pain score of individuals(n=17)
120
100
80
60
40
20
0
Pain score(%)
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

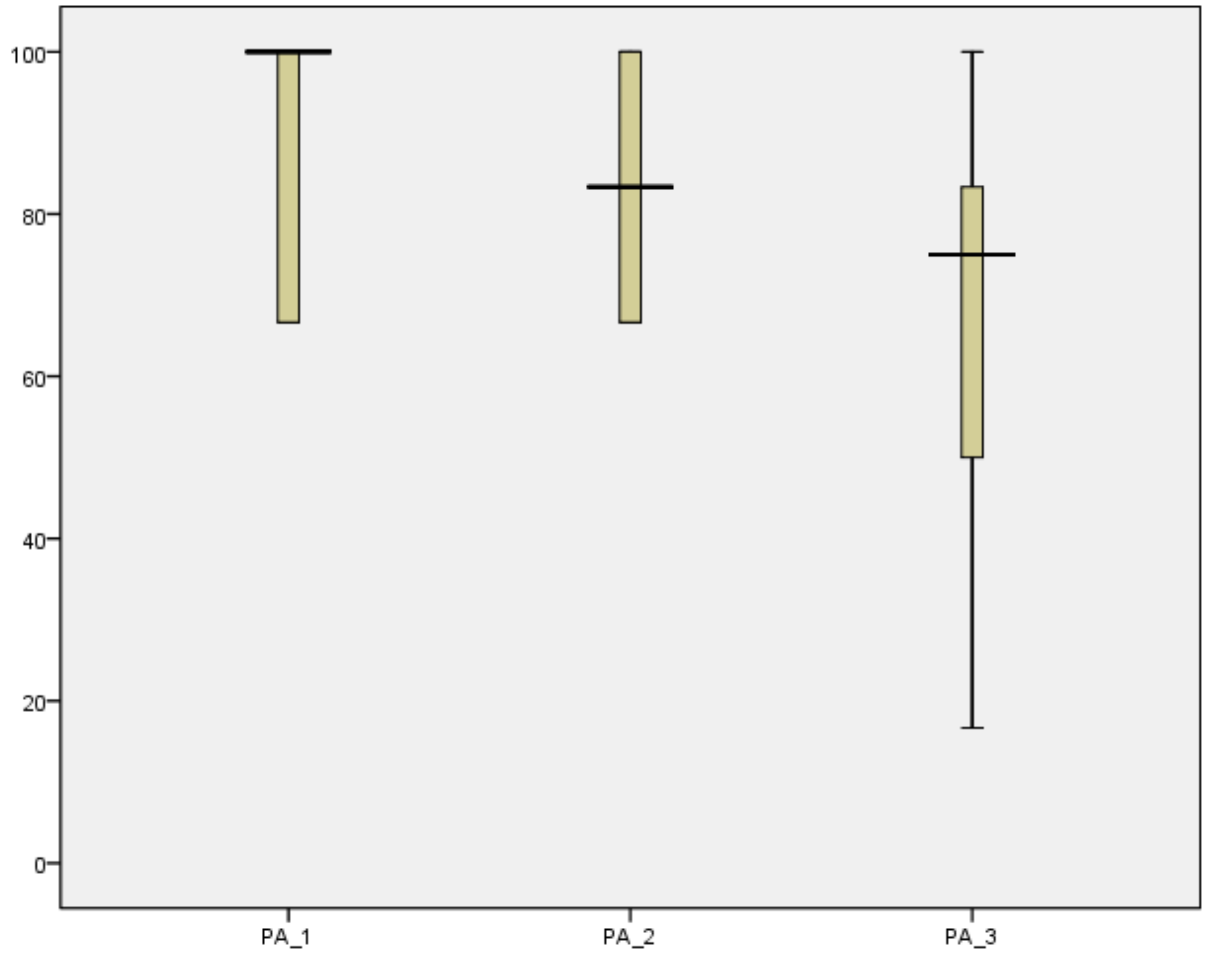
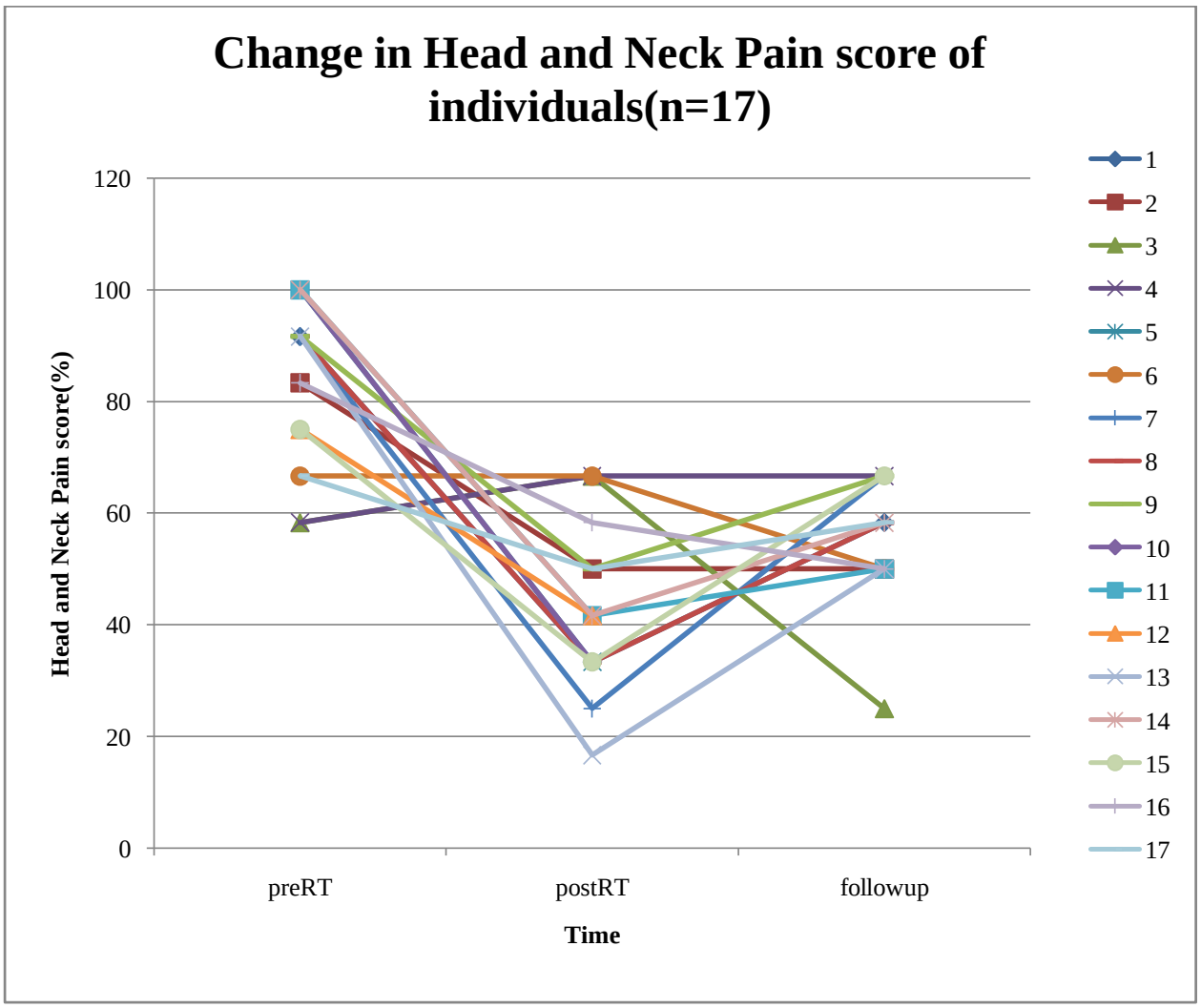


Fig 22: Box plot showing the variation in Pain score (PA) from preRT (PA_1) to postRT (PA_2) and in first follow up (PA_3)


Change in Head and Neck Pain score of individuals(n=17)
Head and Neck Pain score(%)
120
100
80
60
40
20
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

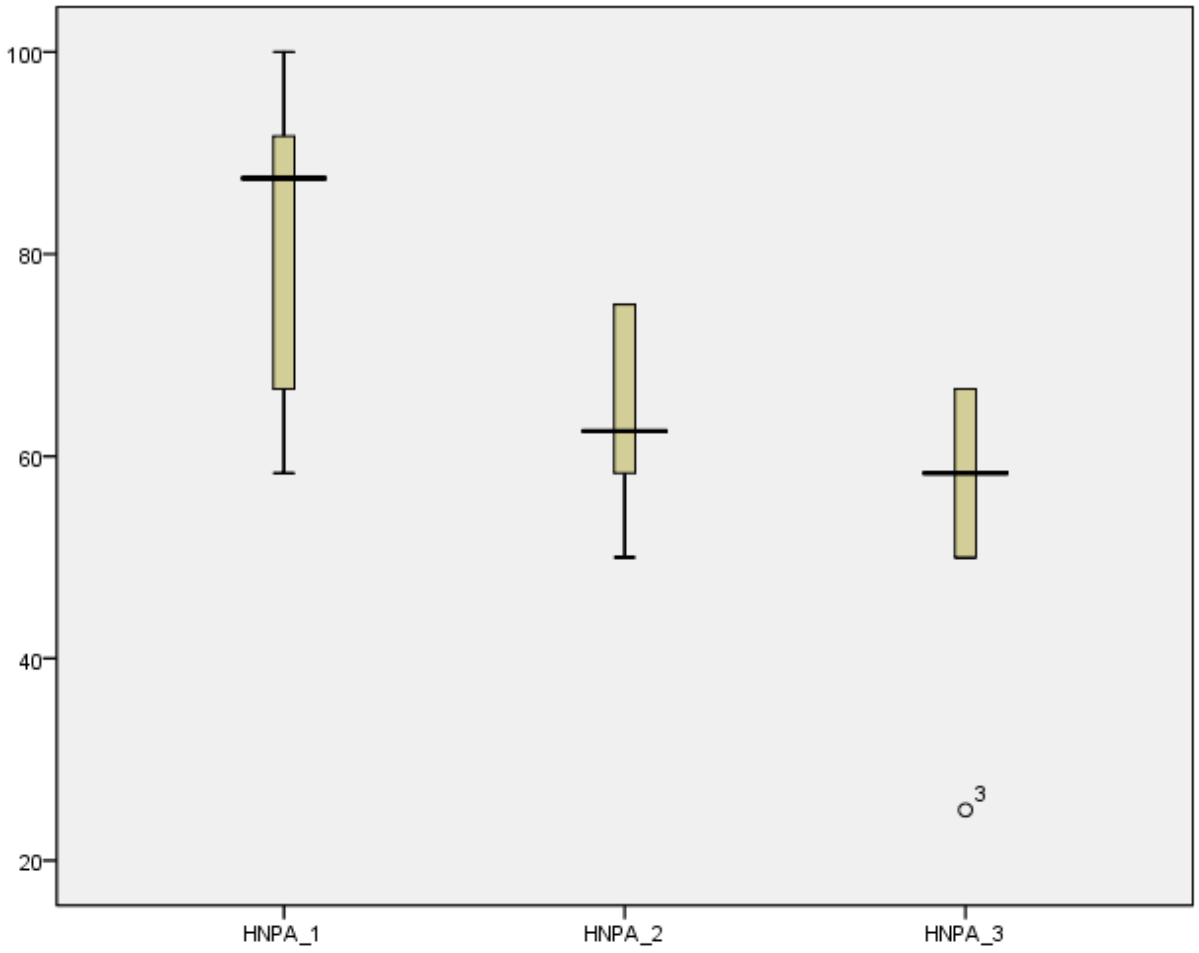
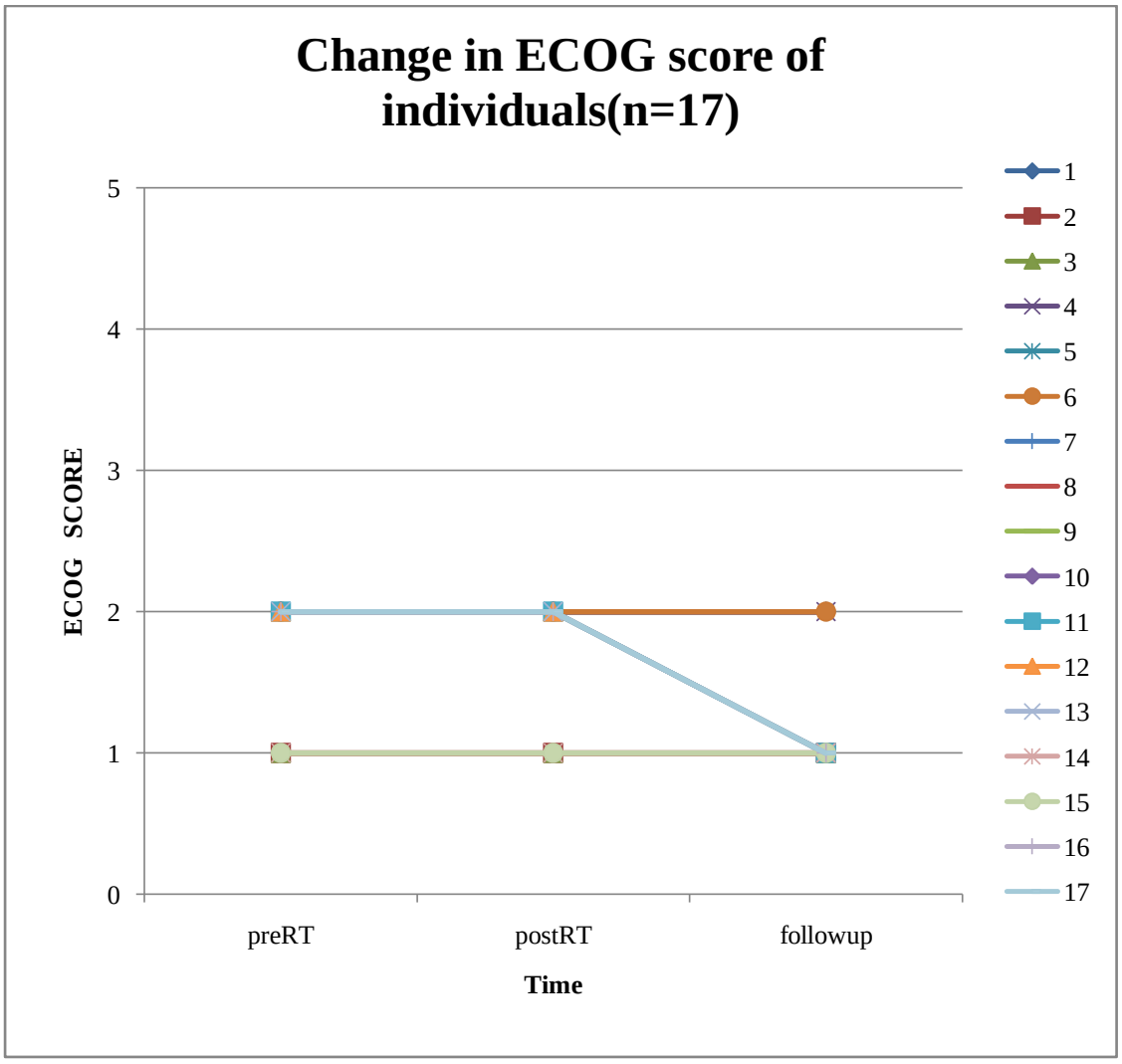
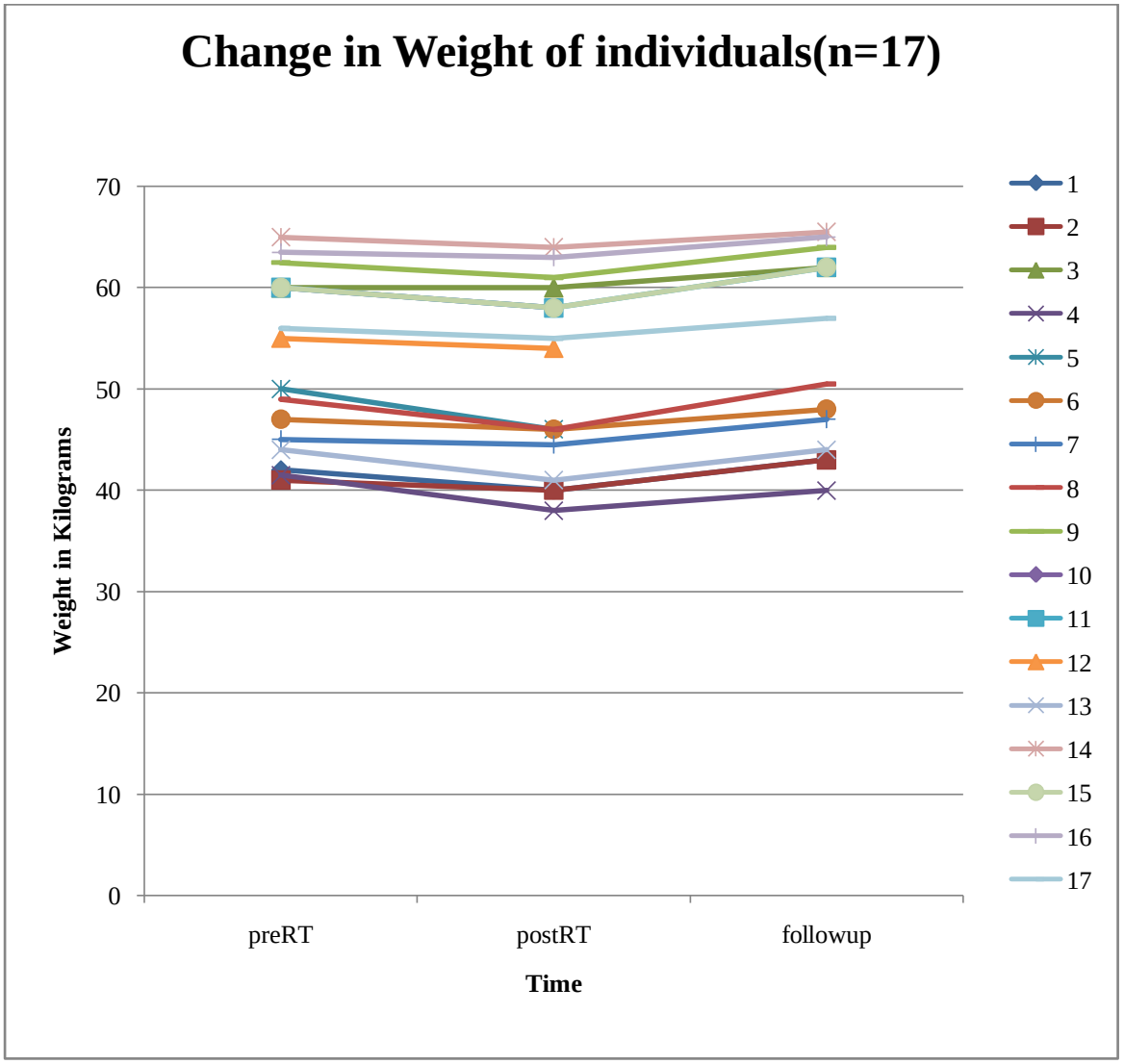


Fig 23: Box plot showing the variation in Head and Neck Pain score (HNPA) from preRT (HNPA_1) to postRT (HNPA_2) and in first follow up (HNPA_3)


Change in ECOG score of individuals(n=17)
ECOG SCORE
5
4
3
2
1
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17


Change in Weight of individuals(n=17)
Weight in Kilograms
70
60
50
40
30
20
10
0
preRT
postRT
followup
Time
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

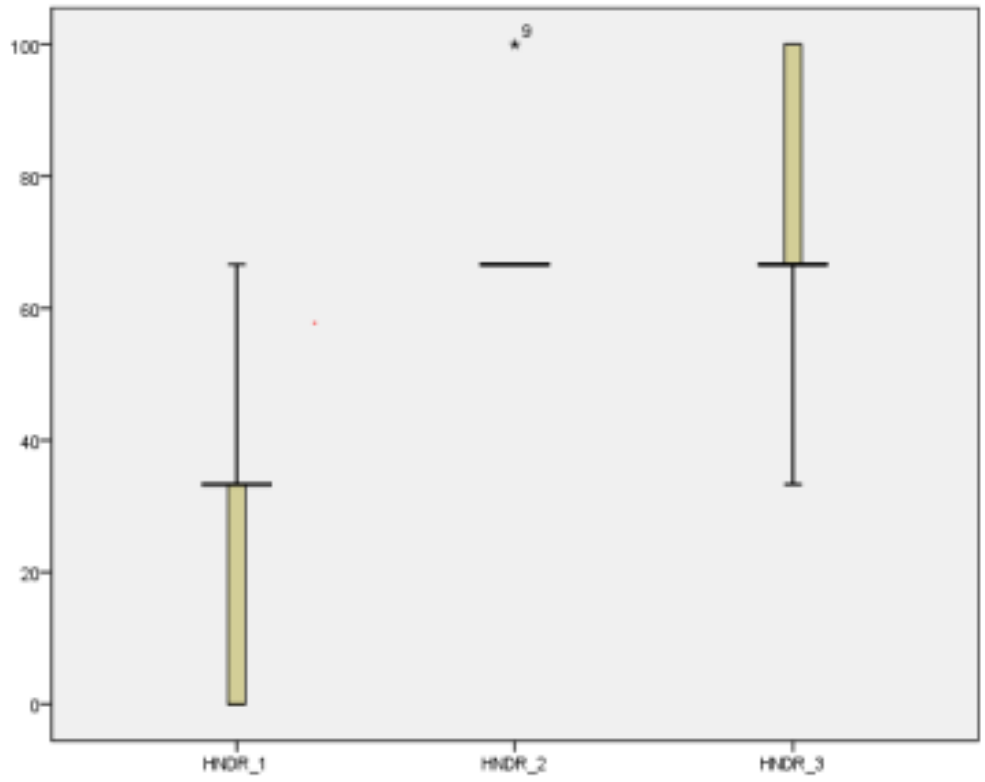


Fig 24: Box plot showing the variation in Dry mouth (HNDR) from preRT (HNDR_1) to postRT (HNDR_2) and in first follow up (HNDR_3)

Discussion

In this study we studied palliation of symptoms in Inoperable Squamous Cell Cancers of the Oral Cavity by a hypofractionated palliative radiotherapy schedule using validated quality of life tools .Our study population consist of seventeen consecutive inoperable oral cavity cancers, who were recruited after getting an informed consent, over a time period of 18 months.

Most of the studies on palliative radiotherapy in head and neck included all the subsites of head and neck in which most common site in most of the studies were oral cavity especially in Indian studies. So we planned to study oral cavity cancers alone. Among the study population tongue was the most common subsite. The stage and histology were similar to other studies which included Stage IVA and squamous cell carcinoma. As seen in other studies there was male predilection which can be attributed to the exposure of risk factors like tobacco and alcohol. Among the fourteen male patients, twelve were using tobacco either in the form of smoking or smokeless or both .Contrary to Western literature where smoking forms the major risk factor, ICMR data addresses smokeless tobacco in the form snuff, chewing as a high risk factor for oral cavity cancers in India. This was evident in our study too. Among the three women included in the study one used smokeless tobacco in the form of betel nut chewing.

Most of our patients in our study were treated with two dimensional conventional parallel opposed lateral technique using Cobalt -60 machine which is the most commonly available treatment modality in Indian centers. Use of conformal radiotherapy and Intensity Modulated Radiotherapy Treatment (IMRT) in a palliative setting is resource intensive and is not a feasible option in India where machine time and financial constraints are the major limiting factors.

Various palliative regimens have been tried in head and neck cancers like 30Gy in 20 Fractions,20Gy in 5 Fractions ,quad shot regimen & the 'Christie regimen'(42). Most of the studies included various regime for different patients (44) but in our study all patients were planned for 50Gy in 20 Fractions. The rationale behind choosing this regimen is the Biological effective dose of this regimen 62.5Gy which is very close to the radical dose of 79.2Gy .Most of the palliative radiotherapy regimens in head and neck are extrapolated from the palliative regimens used in brain metastasis and bone metastasis. Tumor biology of head and neck squamous cell carcinomas are different and use of higher dose as used in our study is required for sustained palliation of symptoms.

Very few studies have used such a high dose; Minatel et al studied 58 patients who received 50Gy in 20 fractions. This study used concurrent bleomycin and delivery of radiotherapy was split into a course of two treatment sessions. Each course consisted of 25 Gy in 10 fractions for 2 weeks duration followed by similar second course with a two weeks gap. Total duration of treatment was six weeks where as in our study it was four

weeks ((Inter quartile range 27-28days).Patient population in the study included all head neck sites and only 25 patients were oral cavity cancers. The symptomatic improvement reported in this study was 81% where as in our study there was statistically significant improvement in global health score from 21 to 50.

In Minatel et al group 93% completed treatment with 21% of them requiring inpatient admissions and Ryles tube insertions where as in our study it was 76% and 35% respectively.

Quality of life indices

Global health status score ,functional scales score and symptom scales score of EORTC QLQ 30 and HN35 prior to radiotherapy, post radiotherapy and six weeks after radiotherapy were analysed using Mean(SD) and Median(IQR) statistics and the Statistical significance was tested using the Non parametric test for the related samples (Friedman's test)

Global Health status : The median values are 21, 50 and 46 at baseline post radiotherapy and first follow-up respectively and was found to be significant($p=0.001$).The variation in global health status is also clinically significant as per the Osoba et al study. GHS was found highly significant.

Functional Scales:

Among the functional scales emotional functioning, cognitive functioning and social functioning were found significant at 1% or 5% alpha level (p=0.009, 0.017, 0.016 respectively) and Physical functioning and Role functioning were significant at 10% alpha level (p=0.150, 0.050 respectively).

There is an increase in Physical functioning quality of life scores also (median are same, but IQR is varying. 30-53, for baseline, 32-53 for post radiotherapy and 33- 62 for follow-up.) , however it is not statistically significant at 5% level(p value = 0.150; Friedman test).Physical functioning includes doing activities like carrying a heavy bag or a suitcase and trouble in walking .As the radiation site is oral cavity and fatigue is one of the most common side effect of radiation, this might have affected physical functioning values.

Role functioning was assessed based on the fact that whether radiation had limited the patient in doing either their work or other daily activities or hobbies. Here also median score 33 remained same at for prior radiotherapy and post radiotherapy and shows a slight improvement to score 50.However inter quartile of role functioning was showing an increasing trend. During radiation a patient may be limited in their work and daily activities especially during third and fourth weeks during which, the toxicities of radiation are at their peak.

Symptom scales : The goal of any palliative radiotherapy regimen is pain control and in our study both pain and head and neck specific pain had significantly reduced over time. Fatigue had increased during radiation and has decreased during first follow-up. The increase in nausea, vomiting and constipation during radiation can be attributed to use of morphine during radiation for pain control

Our results were comparable to a Swedish study which analysed 47 head and neck cancer patients of which 12 were oral cavity cancers (58).They assessed quality of life at baseline, completion of radiotherapy and at follow-up during 3, 6, and 12 months using the questionnaire EORTC QLQ-C30-version and H&N35.In this study most of the functions showed a decreasing trend during radiation and returned to base line within an year as depicted in the figure below(58). Similar to our study dry mouth was a late problem which affected quality of life during follow-up visits. The results on improvement of Nutritional status also showed similar trend in both studies. There was weight loss during radiation which improved during subsequent follow-up visits.

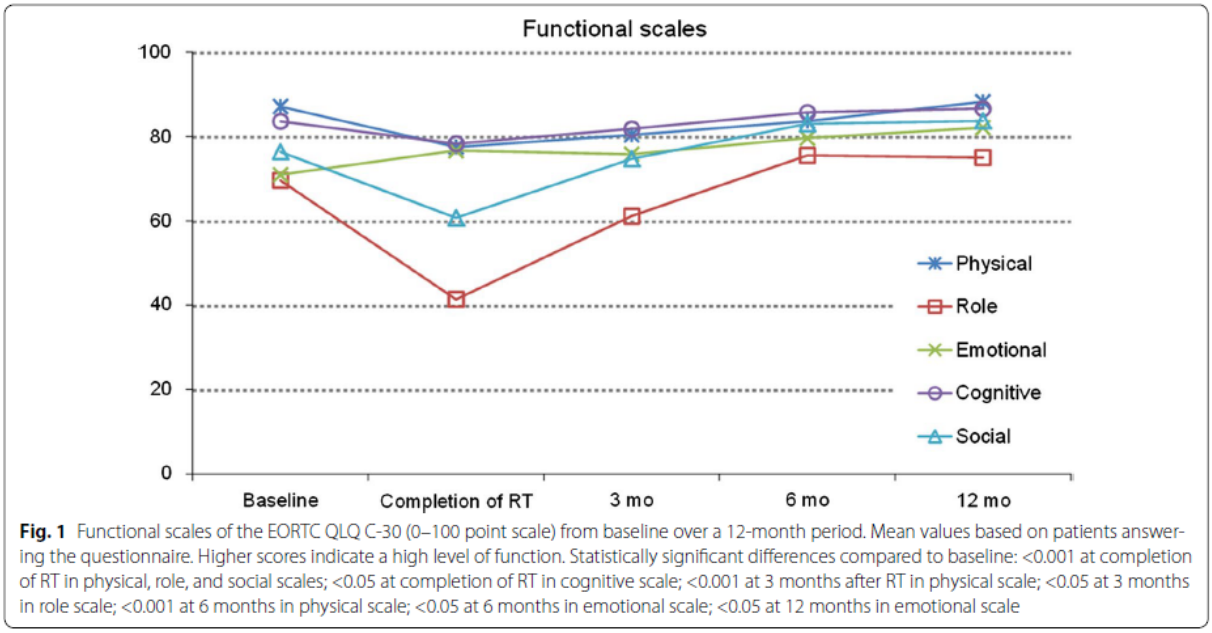


Fig. 1 Functional scales of the EORTC QLQ C-30 (0–100 point scale) from baseline over a 12-month period. Mean values based on patients answering the questionnaire. Higher scores indicate a high level of function. Statistically significant differences compared to baseline: <0.001 at completion of RT in physical, role, and social scales; <0.05 at completion of RT in cognitive scale; <0.001 at 3 months after RT in physical scale; <0.05 at 3 months in role scale; <0.001 at 6 months in physical scale; <0.05 at 6 months in emotional scale; <0.05 at 12 months in emotional scale

Fig 25: Graph adapted from Loorents et al (58) showing variation of functional scales over a period of time

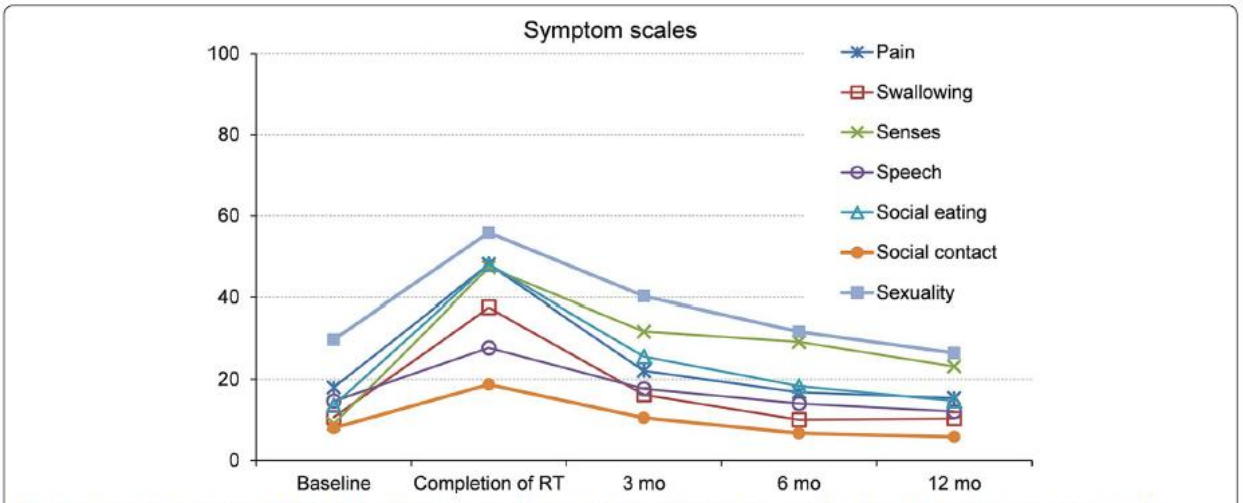


Fig. 3 Symptom scales of the EORTC QLQ-H&N35 (0–100-point scale) from baseline over a 12-month period. Mean values based on patients answering the questionnaire. Higher scores indicate more severe symptoms or impairments. Statistically significant differences compared to baseline: <0.001 at completion of RT in pain, swallowing, senses, social eating, and sexuality; <0.05 at completion of RT in social contact, and speech; <0.001 at 3 months after RT in senses, and social eating; <0.05 at 3 months in sexuality; <0.001 at 6 months in senses; <0.05 at 6 months in social eating; <0.001 at 12 months in senses

Fig 26: Graph adapted from Loorents et al (58) showing variation of symptom scales over a period of time

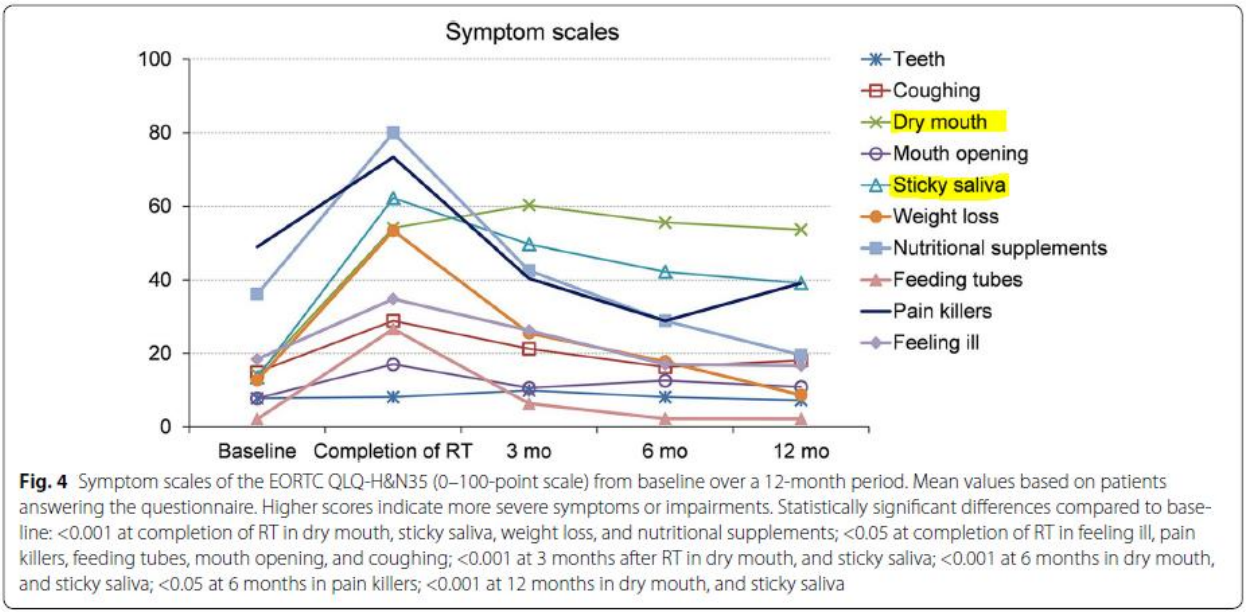


Fig. 4 Symptom scales of the EORTC QLQ-H&N35 (0–100-point scale) from baseline over a 12-month period. Mean values based on patients answering the questionnaire. Higher scores indicate more severe symptoms or impairments. Statistically significant differences compared to baseline: <0.001 at completion of RT in dry mouth, sticky saliva, weight loss, and nutritional supplements; <0.05 at completion of RT in feeling ill, pain killers, feeding tubes, mouth opening, and coughing; <0.001 at 3 months after RT in dry mouth, and sticky saliva; <0.001 at 6 months in dry mouth, and sticky saliva; <0.05 at 6 months in pain killers; <0.001 at 12 months in dry mouth, and sticky saliva

Fig 27: Graph adapted from Loorents et al (58) showing variation of symptom scales over a period of time

Summary and future directions

In patients diagnosed with inoperable oral cavity cancer, hypofractionated radiotherapy delivering 50Gy in 20 fractions over 4 weeks is a well tolerated and safe regimen. In our study statistically significant Quality of life improvement in global health score, social functioning and cognitive functioning lasting for a minimum six weeks was attained after completion of treatment with this regimen .

Based on the results of this study, a continuation of this study with a large sample size is needed. A randomized study using this radiotherapy regime in one arm versus conventional radiotherapy fractionation will be ideal to show the usefulness of this

regime. To create an Indian population based Qol score addressing cultural and ethnic practises of our country will be useful while conducting this study. Identify a subgroup that will benefit from palliative radiotherapy than best supportive care. Studies for the identification of a biomarker which will predict the response to palliative radiotherapy are still not conclusive.

Limitation

The follow up duration was short.

Study with larger sample size would yield more convincing outcomes.

Conclusions

- In patients with inoperable oral cavity cancer, hypofractionated radiotherapy delivering 50Gy in 20 fractions over 4 weeks is an effective, well tolerated and safe regimen.

- Palliative radiotherapy using 2.5Gy per fraction achieved reasonable palliation with good symptom control and acceptable toxicity profile.

- Statistically significant Quality of life improvement lasting for a minimum six weeks was attained after completion of treatment with this regimen.

Bibliography

1. Kaustav Talapatra. Palliative radiotherapy in head and neck cancers: Evidence based review Talapatra K, Gupta T, Agarwal JP, Laskar SG, Shrivastava SK, Dinshaw KA Indian J Palliat Care [Internet]. [cited 2014 Aug 3]. Available from: http://www.jpalliativecare.com/article.asp?issn=0973-1075;year=2006;volume=12;issue=2;spage=44;epage=50;aulast=Talapatra

2. Parkin DM, Stjernswärd J, Muir CS. Estimates of the worldwide frequency of twelve major cancers. Bull World Health Organ. 1984;62(2):163.

3. Fact Sheets by Population [Internet]. [cited 2016 Jul 17]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

4. Stewart BW, Kleihues P, International Agency for Research on Cancer, editors. World cancer report. Lyon: IARC Press; 2003. 351 p.

5. Buccal Mucosa Cancer final pdf 9.6.14.pdf [Internet]. [cited 2015 Oct 18]. Available from: http://www.icmr.nic.in/guide/cancer/Buccal%20Mucosa%20Cancer%20final%20pdf%209.6.14.pdf

6. Coelho KR. Challenges of the Oral Cancer Burden in India. J Cancer Epidemiol. 2012;2012:1–17.

7. Petersen PE. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century–the approach of the WHO Global Oral Health Programme. Community Dent Oral Epidemiol. 2003;31(s1):3–24.

8. Shanta V, Vendhan Gajalakshmi V, Swaminathan R, Rama R. Population based cancer registry, Chennai. Cancer Inst WIA Adyar Chennai Individ Regist Data. 1990;1996:173–94.

9. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec 15;127(12):2893–917.

10. Ko Y-C, Huang Y-L, Lee C-H, Chen M-J, Lin L-M, Tsai C-C. Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. J Oral Pathol Med. 1995;24(10):450–453.

11. Moore GE, Bissinger LL, Proehl EC. Intraoral Cancer and the Use of Chewing Tobacco*. J Am Geriatr Soc. 1953 Jul 1;1(7):497–506.

12. Muwonge R, Ramadas K, Sankila R, Thara S, Thomas G, Vinoda J, et al. Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: A nested case-control design using incident cancer cases. Oral Oncol. 2008 May;44(5):446–54.

13. Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chronic Dis. 1972;25(12):711–716.

14. Lubin JH, Purdue M, Kelsey K, Zhang Z-F, Winn D, Wei Q, et al. Total Exposure and Exposure Rate Effects for Alcohol and Smoking and Risk of Head and Neck Cancer: A Pooled Analysis of Case-Control Studies. Am J Epidemiol. 2009 Oct 15;170(8):937–47.

15. Giovino GA. The tobacco epidemic in the United States. Am J Prev Med. 2007 Dec;33(6 Suppl):S318-326.

16. Hobbs CGL, Sterne J a. C, Bailey M, Heyderman RS, Birchall MA, Thomas SJ. Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg. 2006 Aug;31(4):259–66.

17. Hennessey PT, Westra WH, Califano JA. Human Papillomavirus and Head and Neck Squamous Cell Carcinoma: Recent Evidence and Clinical Implications. J Dent Res. 2009 Apr 1;88(4):300–6.

18. Herrero R. Human Papillomavirus and Oral Cancer: The International Agency for Research on Cancer Multicenter Study. CancerSpectrum Knowl Environ. 2003 Dec 3;95(23):1772–83.

19. Blitzer GC, Smith MA, Harris SL, Kimple RJ. Review of the Clinical and Biologic Aspects of Human Papillomavirus-Positive Squamous Cell Carcinomas of the Head and Neck. Int J Radiat Oncol. 2014 Mar;88(4):761–70.

20. Petti S. Lifestyle risk factors for oral cancer. Oral Oncol. 2009 Apr;45(4–5):340–50.

21. Kademani D. Oral cancer. In: Mayo Clinic Proceedings [Internet]. Elsevier; 2007 [cited 2016 Jul 17]. p. 878–887. Available from: http://www.sciencedirect.com/science/article/pii/S0025619611613153

22. Final Recommendation Statement: Oral Cancer: Screening - US Preventive Services Task Force [Internet]. [cited 2016 Jul 17]. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/oral-cancer-screening1

23. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. N Engl J Med. 2001;345(26):1890–1900.

24. AJCC - American Joint Committee on Cancer [Internet]. [cited 2015 Oct 21]. Available from: https://cancerstaging.org/Pages/default.aspx

25. Joshi P, Dutta S, Chaturvedi P, Nair S. Head and Neck Cancers in Developing Countries. Rambam Maimonides Med J. 2014 Apr 28;5(2):e0009.

26. Quality of Life in Head and Neck Cancer Patients: Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35 [Internet]. [cited 2014 Dec 28]. Available from: http://jco.ascopubs.org/content/17/3/1008.abstract

27. Law CP, Chandra RV, Hoang JK, Phal PM. Imaging the oral cavity: key concepts for the radiologist. Br J Radiol. 2011 Oct;84(1006):944–57.

28. Radiobiology Fractionation Joiner.pdf [Internet]. [cited 2015 Oct 18]. Available from: https://www.astro.org/uploadedFiles/Main_Site/Meetings_and_Events/2013_Spring_Refresher_Course/Meeting_Program/Radiobiology%20Fractionation%20Joiner.pdf

29. Nahum AE. The Radiobiology of Hypofractionation. Clin Oncol. 2015 May;27(5):260–9.

30. Maciejewsi et al. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx: Tumor dose-response and repopulation [Internet]. [cited 2016 Feb 19]. Available from: http://www.sciencedirect.com/science/article/pii/0360301689905038

31. Hall EJ: Radiobiology for the Radiologist. Philadelphia, PA, Lippincott,2000 - Google Scholar [Internet]. [cited 2016 Feb 23]. Available from: https://scholar.google.co.in/scholar?q=Hall+EJ:+Radiobiology+for+the+Radiologist.+Philadelphia,+PA,+Lippincott,2000&hl=en&as_sdt=0&as_vis=1&oi=scholart&sa=X&ved=0ahUKEwifscTKwo3LAhWNHI4KHXBSAhwQgQMIHTAA

32. Pajonk F, Vlashi E, McBride WH. Radiation Resistance of Cancer Stem Cells: The 4 R's of Radiobiology Revisited. STEM CELLS. 2010 Feb 4;28(4):639–48.

33. Slide 1 - HypofractionationMarples.pdf [Internet]. [cited 2014 Nov 2]. Available from: https://www.astro.org/uploadedFiles/Main_Site/Meetings_and_Events/2014_Spring_Refresher_Course/Meeting_Program/HypofractionationMarples.pdf

34. Withers HR. Biologic basis for altered fractionation schemes. Cancer. 1985 May 1;55(S9):2086–95.

35. Dale RG. The application of the linear-quadratic model to fractionated radiotherapy when there is incomplete normal tissue recovery between fractions, and possible implications for treatments involving multiple fractions per day. Br J Radiol. 1986 Sep;59(705):919–27.

36. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. Br J Radiol. 1985 Jun 1;58(690):515–28.

37. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989 Aug 1;62(740):679–94.

38. Brenner DJ. The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction. Semin Radiat Oncol. 2008 Oct;18(4):234–9.

39. Fowler JF. 21 years of Biologically Effective Dose. Br J Radiol. 2010 Jul;83(991):554–68.

40. Hodson et al. The Role of Palliative Radiotherapy In Advanced Head and Neck Cancer | Ian Hodson - Academia.edu [Internet]. [cited 2016 Feb 24]. Available from: http://www.academia.edu/376393/The_Role_of_Palliative_Radiotherapy_In_Advanced_Head_and_Neck_Cancer

41. NCCN guidelines. [cited 2014 Jul 27]. Available from: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

42. Al-mamgani A, Tans L, Van rooij PHE, Noever I, Baatenburg de jong RJ, Levendag PC. Hypofractionated radiotherapy denoted as the “Christie scheme”: An effective means of palliating patients with head and neck cancers not suitable for curative treatment. Acta Oncol. 2009 Jan;48(4):562–70.

43. Lok BH, Jiang G, Gutiontov S, Lanning RM, Sridhara S, Sherman EJ, et al. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. Oral Oncol. 2015 Oct;51(10):957–62.

44. Stevens CM, Huang SH, Fung S, Bayley AJ, Cho JB, Cummings BJ, et al. Retrospective Study of Palliative Radiotherapy in Newly Diagnosed Head and Neck Carcinoma. Int J Radiat Oncol. 2011 Nov;81(4):958–63.

45. Mohanthy,AIIMS. Short course palliative radiotherapy of 20Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study [Internet]. [cited 2014 Jul 27]. Available from: http://www.sciencedirect.com/science/article/pii/S0167814004001392

46. Porceddu SV et al. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment--"Hypo Trial". - PubMed - NCBI [Internet]. [cited 2016 Feb 23]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18036689

47. Paliwal R, Kumar-Patidar A, Walke R, Hirapara P, Jain S, Raj-Bardia M. Palliative Hypo-fractionated Radiotherapy in Locally Advanced Head and Neck Cancer with Fixed Neck Nodes. Iran J Cancer Prev. 2012;5(4):178.

48. Talapatra K, Gupta T, Agarwal JP, Laskar SG, Shrivastava SK, Dinshaw KA, et al. Palliative radiotherapy in head and neck cancers: Evidence based review. Indian J Palliat Care. 2006;12(2):44.

49. WHO measuring QOL [Internet]. [cited 2016 Feb 24]. Available from: http://www.who.int/mental_health/media/68.pdf

50. Ojo B, Genden EM, Teng MS, Milbury K, Misiukiewicz KJ, Badr H. A systematic review of head and neck cancer quality of life assessment instruments. Oral Oncol. 2012 Oct;48(10):923–37.

51. Aaronson AN et. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in on... - PubMed - NCBI [Internet]. [cited 2016 Feb 25]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8433390

52. Scott N, Fayers P, Aaronson N, Bottomley A, de Graeff A, Groenvold M, et al. EORTC QLQ-C30. Ref Values Bruss EORTC [Internet]. 2008 [cited 2016 Feb 24]; Available from: http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual 2008.pdf

53. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. J Clin Oncol. 1999;17(3):1008–1008.

54. Brooks R. Brooks R (1996). EuroQol: the current state of play. Health Policy 37(1):53-72. [Internet]. [cited 2016 Feb 24]. Available from: https://scholar.google.co.in/scholar?q=2.%09Brooks+R+(1996).+EuroQol:+the+curr

ent+state+of+play.+Health+Policy+37(1):53-72.&hl=en&as_sdt=0&as_vis=1&oi=scholart&sa=X&ved=0ahUKEwj6pfjKgJDLAhUFuo4KHc8FB98QgQMIGjAA

55. Group E. EuroQol--a new facility for the measurement of health-related quality of life. - PubMed - NCBI [Internet]. [cited 2016 Feb 24]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10109801

56. Rabin R, Charro F de. EQ-SD: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337–343.

57. CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf [Internet]. [cited 2016 Feb 24]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf

58. Loorents V, Rosell J, Salgado Willner H, Börjeson S. Health-related quality of life up to 1 year after radiotherapy in patients with head and neck cancer (HNC). SpringerPlus [Internet]. 2016 Dec [cited 2016 Sep 14];5(1). Available from: http://springerplus.springeropen.com/articles/10.1186/s40064-016-2295-1

APPENDIX-1

Department of Radiotherapy

CMC Hospital Vellore, Tamil Nadu

Informed consent sheet No:

Title of Research -

To study palliation of symptoms by a hypofractionated radiotherapy schedule in Inoperable Squamous Cell Cancers of the Oral cavity.

Person carrying out the research: Dr Arun Krishnan .M.P

Part I: - Information sheet

Introduction-I am Dr Arun Krishnan .M.P, post graduate student in the department of Radiotherapy. I am doing a research on symptom relief in palliative radiotherapy schedule in locally Advanced Inoperable mouth cancer patients. I am going to give you the information regarding my study and invite you to be a part it. At any point of time if there is any doubt or you are not clear with the study protocol please feel free to ask.

Purpose of the research: Patients with locally advanced mouth cancers similar to your type of cancer will have complaints of pain, difficulty in swallowing, opening of the mouth, speaking & chewing as well as anxiety about the cancer. We try to relieve these symptoms with radiation in a short period of time. You will be asked to grade your symptoms by filling up a questionnaire before starting of treatment and after treatment and during your first follow up visits. We wish to see how much& for how long you are relieved of your symptoms with this short duration radiotherapy treatment schedule.

Participant Selection: You have been invited to participate in this study because **y**ou have been diagnosed to have mouth cancer which is inoperable and through this study we will be able to assess your symptomatic relief by this short radiotherapy schedule.

Voluntary participation: Your participation in this study is entirely

voluntary. Your decision not to take part will not affect your treatment in any way. You may even change your mind and withdraw even if you had agreed to take part earlier.

Information on the Research study: The patients included in the study are locally advanced inoperable mouth cancer patients who are treated with a short radiotherapy schedule. There are various short radiotherapy schedules for advanced head and neck malignancies which deliver radiation using different schedules. You will be treated with a schedule which delivers radiotherapy dose 50Gy in 20 sittings over 4 weeks. Before starting you have to answer a questionnaire regarding your symptoms and present quality of life. After starting treatment you have to answer the same questionnaire at end of 4 weeks and during the first follow up visit which is usually after 4-6 weeks after the end of treatment. The questions focus on your physical symptoms, physical functioning, and social function. Specifically, it also asks you about pain, appearance, activity level, recreation, and swallowing, chewing, speech, taste, and saliva production and about emotional function. By collecting and analysing this information, we will be able to measure the relief of patient's symptoms before and after radiation therapy with this regimen and assess duration of relief of symptoms and response of tumor .The rest of your treatment will continue as other patients being treated in CMC.

Side effects: Since this study only asks you to answer questions about your symptoms, there is no risk for you from this.

Risks: There are no risks to the patients.

Benefits: In India where most of head and neck cancers are detected in an advanced stage the knowledge regarding the amount of symptomatic relief and quality of life improvement that a patient can attain by this regimen of short radiotherapy will be useful. This will used for counseling future group of patients regarding improvement in

symptoms and for appropriate selection of patients being treated with this radiotherapy schedule.

Confidentiality: Your name will not be mentioned anywhere in the datasheet or the final published study. Your data will bear a study number and the same number will be used till analysis**.**

Sharing of the result: The result of research is the property of Christian Medical College and I am entitled to publish it in a journal or at a conference.

Right to refuse or withdraw: You do not have to participate in this research if you do not wish to. It is your choice and all your rights will be respected.

This study has been reviewed by [IRB, Christian Medical College], which is a committee whose task is to make sure that research participants are protected from harm. If you wish to find more about the IRB

Contact:

Institutional Review Board,

Christian Medical College

Office of Research, I st Floor, Carman Block, Bagayam, Vellore 632002 India.

E-mail: research@cmcvellore.ac.in.

Tel: 0416 -2284294, 2284202 Fax: 0416 – 2262788, 2284481.

It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study.

PART II: Informed Consent form to participate in a research study

Study Title : To study palliation of symptoms by a hypofractionated radiotherapy schedule in Inoperable Squamous Cell Cancers of the Oral cavity.

Study Number: _____

Subject's Initials: _____

Subject's Name:

_____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the investigators conducting this trial, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

(v) I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally

Acceptable

Date: _____/_____/_____

Signatory's Name: _____

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

RT_NUMBER	AGE	SEX	LAST_FOLLOWUP	DATE_DIAG	DAYS_OF_FO	TNM	Tstage	Nstage	NODALL	Mstage	STAGE	SITE
1333/15	63	0	01-Sep-2016	12-Aug-2015	12.68	T4aN0M0	4.00	0.00	0	0.00	4.00	3
253/15	56	0	01-Sep-2016	20-Feb-2015	18.37	T4aN2bM0	4.00	2.00	2	0.00	4.00	7
646/14	35	0	01-Sep-2016	07-May-2015	15.87	T4aN2bM0	4.00	2.00	1	0.00	4.00	3
749/15	71	0	01-Sep-2016	16-Jun-2015	14.55	T4aN1M0	4.00	1.00	1	0.00	4.00	3
	43	0	#NULL!	27-Jul-2015	#NULL!	T4N3M0	4.00	3.00	1	0.00	5.00	5
1126/15	48	0	01-Sep-2016	10-Sep-2015	11.73	T4aN1M0	4.00	1.00	1	0.00	4.00	3
102/16	54	1	01-Sep-2016	14-Jan-2016	7.59	T4aN2bM0	4.00	2.00	1	0.00	4.00	3
1307/15	58	0	01-Sep-2016	20-Oct-2015	10.41	T4aN2cM0	4.00	2.00	2	0.00	4.00	3
1455/15	48	0	01-Sep-2016	21-Nov-2015	9.36	T4bN2bM0	4.00	2.00	2	0.00	5.00	3
1552/15	66	1	#NULL!	16-Dec-2015	#NULL!	T4aN2bM0	4.00	2.00	3	0.00	4.00	3
52/16	55	0	01-Sep-2016	30-Dec-2015	8.08	T4bN2bM0	4.00	2.00	1	0.00	5.00	5
153/16	69	0	#NULL!	01-Feb-2016	#NULL!	T4bN0M0	4.00	0.00	0	0.00	4.00	5
396/16	57	0	01-Sep-2016	18-Mar-2016	5.49	T4aN0M0	4.00	0.00	0	0.00	4.00	4
682/16	44	0	01-Sep-2016	22-Apr-2016	4.34	T4N3M0	4.00	3.00	3	0.00	5.00	3
527/16	51	1	01-Sep-2016	29-Apr-2016	4.11	T4N0M0	4.00	0.00	0	0.00	4.00	11
714/16	51	0	01-Sep-2016	18-Jun-2016	2.46	T4N0M0	4.00	0.00	0	0.00	4.00	5
756/16	51	0	01-Sep-2016	22-Jun-2016	2.33	T4bN2cM0	4.00	2.00	1	0.00	5.00	5

SYMPTOM	ALCOHOL	TOBACC	CT_MRI	STARTING	COMPLETION	date_diff1	FIRST_FOLLOWUP	LASTFOLLOWUP	morphine	CANDIDAIASIS	GEFITINIB	GCSF
2.00	1.00	1	1.00	05-Nov-2015	03-Dec-2015	28.00	05-Feb-2016	19-Jul-2016	1.00	1.00	0.00	0.00
2.00	0.00	3	0.00	27-Feb-2015	26-Mar-2015	27.00	14-Oct-2015	14-Oct-2015	0.00	0.00	0.00	0.00
2.00	0.00	2	1.00	28-May-2015	24-Jun-2015	27.00	05-Aug-2015	13-Jan-2016	0.00	0.00	1.00	0.00
2.00	0.00	0	0.00	19-Jun-2015	16-Jul-2015	27.00	07-Sep-2015	09-Sep-2015	0.00	1.00	0.00	0.00
2.00	0.00	2	0.00	04-Aug-2015	11-Aug-2015	#NULL!	#NULL!	#NULL!	1.00	0.00	0.00	0.00
2.00	0.00	0	1.00	18-Sep-2015	15-Oct-2015	27.00	23-Dec-2015	23-Dec-2015	1.00	1.00	1.00	0.00
2.00	0.00	0	1.00	29-Jan-2016	23-Feb-2016	25.00	20-Apr-2016	20-Apr-2016	0.00	0.00	1.00	1.00
2.00	0.00	1	1.00	29-Oct-2015	25-Nov-2015	27.00	15-Feb-2016	15-Feb-2016	0.00	0.00	0.00	0.00
2.00	0.00	3	1.00	01-Dec-2015	30-Dec-2015	29.00	10-Feb-2016	08-Feb-2016	0.00	1.00	0.00	1.00
2.00	0.00	2	0.00	24-Dec-2015	31-Dec-2015	7.00	26-Feb-2016	26-Feb-2016	0.00	0.00	0.00	0.00
2.00	0.00	3	1.00	14-Jan-2016	16-Feb-2016	33.00	16-Feb-2016	16-Feb-2016	1.00	1.00	0.00	0.00
2.00	0.00	0	1.00	08-Feb-2016	#NULL!	#NULL!	24-Feb-2016	24-Feb-2016	1.00	1.00	0.00	0.00
2.00	1.00	3	0.00	14-Apr-2016	19-May-2016	35.00	19-May-2016	19-May-2016	0.00	1.00	0.00	1.00
2.00	1.00	3	1.00	16-Jun-2016	13-Jul-2016	27.00	13-Jul-2016	13-Jul-2016	1.00	1.00	0.00	0.00
9.00	0.00	0	1.00	10-May-2016	06-Jun-2016	27.00	25-Jul-2016	25-Jul-2016	1.00	1.00	0.00	0.00
2.00	0.00	2	0.00	21-Jun-2016	18-Jul-2016	27.00	#NULL!	#NULL!	0.00	1.00	0.00	0.00
9.00	0.00	3	1.00	01-Jul-2016	29-Jul-2016	28.00	#NULL!	#NULL!	1.00	0.00	0.00	0.00

NGFEEDS	RT_status	no_of_frac	Y_NOT	ADMISON	INOPERABILTY	TECHNIQUE	BREAKS	Y_BREAK	recurrence	FF_RESPON	FAILURE	Typeoftreatment
1.00	1	20.00	0.00	0.00	2.00	1.00	0	0	1.00	1.00	0.00	0.00
0.00	1	20.00	0.00	1.00	2.00	1.00	0	0	1.00	1.00	0.00	1.00
0.00	1	20.00	0.00	0.00	2.00	1.00	0	0	1.00	1.00	0.00	1.00
0.00	1	20.00	0.00	0.00	2.00	1.00	0	0	1.00	1.00	0.00	0.00
0.00	2	16.00	1.00	1.00	4.00	1.00	0	0	#NULL!	#NULL!	#NULL!	#NULL!
1.00	1	20.00	0.00	0.00	2.00	1.00	0	0	1.00	1.00	0.00	4.00
0.00	2	16.00	2.00	0.00	2.00	1.00	1	1	1.00	1.00	0.00	4.00
0.00	1	20.00	0.00	0.00	2.00	1.00	0	0	1.00	1.00	0.00	1.00
0.00	1	20.00	0.00	1.00	2.00	1.00	1	1	1.00	1.00	0.00	1.00
0.00	2	#NULL!	1.00	0.00	2.00	1.00	0	0	1.00	#NULL!	0.00	#NULL!
1.00	1	20.00	0.00	1.00	2.00	1.00	1	1	1.00	#NULL!	0.00	#NULL!
1.00	2	14.00	2.00	1.00	2.00	1.00	1	4	1.00	#NULL!	0.00	#NULL!
1.00	1	20.00	0.00	1.00	2.00	1.00	1	1	1.00	#NULL!	0.00	#NULL!
1.00	1	20.00	0.00	0.00	4.00	1.00	0	0	1.00	#NULL!	0.00	#NULL!
0.00	1	20.00	0.00	0.00	2.00	1.00	0	0	1.00	1.00	0.00	#NULL!
0.00	1	20.00	0.00	0.00	2.00	1.00	0	0	1.00	1.00	0.00	#NULL!
0.00	1	20.00	0.00	0.00	4.00	1.00	0	0	1.00	#NULL!	0.00	#NULL!

LF_DETAILS	Currentstatus	Expireddate	gap_time	wt_pre	wt_post	wt_diff	wt_FF	preskin	postskin	FFskin	premuco	postmuco
BLEEDING FRM ORAL	1	#NULL!	0	42.0	40.0	-4.76	43.0	9	2	9	9	3
PALCHEMO		#NULL!	0	41.0	40.0	-2.44	43.0	9	9	9	9	9
GEFITNIB	1	#NULL!	0	60.0	60.0	0.00	62.0	9	2	9	9	5
CANDIASIS+	1	#NULL!	0	41.5	38.0	-8.43	40.0	9	2	9	2	2
		#NULL!	0	50.0	46.0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!
GEFITINIB		#NULL!	0	47.0	46.0	-2.13	48.0	9	1	9	9	2
GEFITINIB	1	#NULL!	3	45.0	44.5	-1.11	47.0	9	3	9	9	3
PALCHEMOAT HOMETOWN	2	#NULL!	0	49.0	46.0	-6.12	50.5	9	2	1	9	2
PALCHEMOAT HOMETOWN	1	#NULL!	3	62.5	61.0	-2.40	64.0	9	2	2	9	2
NO FF_LF		#NULL!	0	60.0	58.0	#NULL!	#NULL!	9	9	#NULL!	9	9
NO LF	1	#NULL!	3	60.0	58.0	-3.33	62.0	9	2	9	9	3
NI FF_LF	0	#NULL!	1	55.0	54.0	#NULL!	#NULL!	9	9	#NULL!	9	9
NO LF	1	#NULL!	3	44.0	41.0	-6.82	44.0	9	2	#NULL!	9	3
NO LF	1	#NULL!	0	65.0	64.0	-1.54	65.5	9	2	#NULL!	9	3
NO LF	2	#NULL!	0	60.0	58.0	-3.33	62.0	9	1	#NULL!	9	2
NO LF	1	#NULL!	0	63.5	63.0	-0.79	65.0	9	1	#NULL!	9	2
		#NULL!	0	56.0	55.0	#NULL!	57.0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!

FFmuco	prexero	postxero	FF_xero	pre_dysph	post_dysph	FF_dysph	PRE_ECOG	POST_ECOG	FF_ECOG	REMARKS	HISTOLOGY	Dateof_Distantmets
9	9	9	9	9	9	9	2.00	2.00	2.00	SEIZURE	1	#NULL!
9	9	9	9	9	9	9	1.00	1.00	1.00		1	#NULL!
9	9	9	9	9	9	0	1.00	1.00	1.00	ANKYLOGLOSSIA	1	#NULL!
9	9	9	9	9	2	9	2.00	2.00	2.00	pacemaker	1	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!		1	#NULL!
9	9	9	9	9	9	9	2.00	2.00	2.00		1	#NULL!
9	9	9	9	9	9	9	2.00	2.00	1.00	REACTION-LIPSHEILD-GCSF-	1	#NULL!
9	9	9	9	9	9	9	1.00	1.00	1.00		1	#NULL!
9	9	9	9	9	9	9	2.00	2.00	1.00	REACTION-GCSF	1	#NULL!
#NULL!	9	9	#NULL!	9	9	#NULL!	2.00	2.00	#NULL!		1	#NULL!
#NULL!	9	9	#NULL!	9	9	9	2.00	2.00	1.00	REACTION	1	#NULL!
#NULL!	9	9	#NULL!	9	9	#NULL!	2.00	2.00	#NULL!	EDEMA/THROMBUS	1	#NULL!
#NULL!	9	9	#NULL!	9	9	#NULL!	2.00	2.00	1.00	REACTION	1	#NULL!
#NULL!	9	9	#NULL!	9	9	#NULL!	1.00	1.00	1.00		1	#NULL!
#NULL!	9	9	9	9	9	9	1.00	1.00	1.00	NO FF	1	#NULL!
#NULL!	9	9	#NULL!	9	9	#NULL!	2.00	2.00	1.00	NO FF	1	#NULL!
#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	2.00	2.00	1.00		1	#NULL!

SALVAGESURG	DURATION	Dateofrecurrence	wt_loss	wt_loss_percent	Dateof_LocalProg	Dateof_RegionalPrg	gap_dur	DURATIONOFSYMT	QU1_1	QU2_1	QU3_1	QU4_1
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	3	1	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	1	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	2	1	1
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	3	1	2
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	3	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	1	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	1.00	#NULL!	4	4	1	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	2	1	2
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	2	1	2
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	3	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	3	4
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	3	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	3	4
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	2	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	4	2	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	3	1	3
0	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	#NULL!	4	3	1	3

QU5_1	QU6_1	QU7_1	QU8_1	QU9_1	QU10_1	QU11_1	QU12_1	QU13_1	QU14_1	QU15_1	QU16_1	QU17_1
3	3	3	1	4	3	3	3	2	3	3	1	2
3	3	3	1	3	2	3	2	3	3	2	3	1
1	2	3	1	3	2	2	3	2	2	2	1	1
2	3	2	1	3	2	2	3	2	3	2	1	1
4	4	4	1	4	4	4	4	4	3	3	1	1
2	2	2	1	3	2	2	3	2	2	2	1	1
3	2	2	1	3	2	3	3	4	2	1	1	1
3	3	3	1	4	3	3	4	4	2	3	2	1
3	3	3	1	4	3	2	2	3	3	3	1	1
3	4	4	1	4	3	4	4	2	3	3	1	1
4	4	4	2	4	3	4	3	4	3	3	1	1
4	4	3	1	4	4	2	4	2	4	4	3	1
4	4	4	1	4	4	2	4	3	3	2	3	1
4	4	4	1	4	3	3	4	4	4	3	1	1
2	3	2	1	4	4	2	3	4	4	3	2	1
3	3	3	1	4	3	3	3	3	3	3	1	1
3	2	3	1	4	4	2	3	3	3	3	2	1

QU18_1	QU19_1	QU20_1	QU21_1	QU22_1	QU23_1	QU24_1	QU25_1	QU26_1	QU27_1	QU28_1	QU29_1	QU30_1
4	4	3	4	4	4	4	3	3	3	4	3	3
2	3	3	4	4	3	4	3	3	2	2	2	3
3	3	2	3	3	3	3	3	3	3	4	4	4
3	3	3	2	2	2	2	3	3	3	2	4	4
4	4	4	4	4	4	4	4	4	4	4	1	1
3	3	2	3	3	3	3	3	3	3	4	5	5
4	3	3	4	4	3	3	3	3	4	4	3	3
3	4	3	3	3	3	3	3	3	3	4	2	2
4	4	3	3	3	3	3	4	4	3	2	2	2
4	4	3	3	3	3	3	3	4	4	4	1	1
4	4	4	4	4	4	4	4	4	4	2	1	1
3	4	2	4	4	4	4	4	4	4	2	2	2
4	4	2	3	3	3	3	4	4	4	4	1	2
3	4	3	4	4	3	4	3	3	4	4	1	1
4	4	3	3	3	3	3	4	3	3	4	3	3
2	4	4	4	4	4	4	3	4	3	3	2	2
4	4	4	3	3	3	3	3	3	3	4	2	2

QU31_1	QU32_1	QU33_1	QU34_1	QU35_1	QU36_1	QU37_1	QU38_1	QU39_1	QU40_1	QU41_1	QU42_1	QU43_1
4	3	4	4	3	3	4	2	3	4	1	4	2
3	4	3	4	3	3	3	2	2	3	1	3	3
3	2	3	3	2	3	3	1	2	3	2	3	2
3	2	3	3	2	3	4	1	2	3	2	3	2
4	4	4	4	3	4	4	2	4	4	2	4	4
3	2	3	4	2	3	2	1	2	3	2	3	2
4	3	4	4	3	3	3	2	3	4	1	4	3
4	3	4	4	3	3	4	1	3	4	2	3	3
4	3	4	4	3	3	4	2	2	3	1	3	3
4	4	4	4	4	4	4	2	3	3	2	4	3
4	4	4	4	4	4	4	2	4	3	3	4	4
4	3	3	3	3	3	4	1	4	4	3	1	4
4	4	3	4	4	4	4	1	4	4	3	3	4
4	4	4	4	3	4	4	1	3	4	3	1	4
4	3	3	3	3	4	4	2	3	4	2	3	3
3	4	3	4	3	4	4	1	3	3	2	3	3
4	2	3	3	3	4	4	2	3	3	1	4	3

QU44_1	QU45_1	QU46_1	QU47_1	QU48_1	QU49_1	QU50_1	QU51_1	QU52_1	QU53_1	QU54_1	QU55_1	QU56_1
3	3	3	4	4	3	2	3	3	3	3	3	3
3	3	3	4	4	3	2	3	3	3	3	2	4
2	2	2	3	3	3	2	3	3	1	1	2	3
2	3	2	4	4	2	1	2	2	2	2	2	3
3	3	3	4	3	4	2	4	4	3	3	4	3
2	2	2	3	3	2	1	3	2	3	3	2	2
3	3	2	4	4	3	2	4	3	2	2	2	3
3	4	3	4	4	3	2	3	3	2	2	2	3
3	3	2	4	4	3	2	3	3	3	3	2	3
3	4	3	4	4	4	2	3	4	3	4	2	4
4	3	3	4	4	4	2	4	4	4	4	2	4
3	3	2	4	3	3	1	3	3	4	4	2	3
3	4	3	4	4	4	2	3	4	3	3	3	3
4	3	3	4	4	4	2	4	4	4	4	3	4
3	3	2	4	3	4	2	4	4	2	2	3	3
3	3	3	4	4	3	2	4	3	3	4	2	3
3	3	3	4	3	3	2	4	3	3	3	3	4

QU57_1	QU58_1	QU59_1	QU60_1	QU61_1	QU62_1	QU63_1	QU64_1	QU65_1	GHS_RS_1	GHS_1	PF2_RS_1	PF2_1
4	2	#NULL!	#NULL!	2	1	1	2	1	3.00	33.33	2.80	40.00
4	3	#NULL!	#NULL!	1	1	1	2	1	2.50	25.00	3.00	33.33
3	2	1	#NULL!	1	1	1	2	1	4.00	50.00	1.80	73.33
4	2	#NULL!	#NULL!	2	1	1	2	1	4.00	50.00	2.40	53.33
3	3	#NULL!	#NULL!	1	1	1	2	1	1.00	0.00	3.60	13.33
3	2	1	#NULL!	1	1	1	2	1	5.00	66.67	2.80	40.00
3	2	2	2	1	1	1	2	1	3.00	33.33	3.00	33.33
4	2	2	3	2	1	1	2	1	2.00	16.67	2.40	53.33
4	2	#NULL!	#NULL!	1	1	1	2	1	2.00	16.67	2.40	53.33
4	2	#NULL!	#NULL!	1	1	1	2	1	1.00	0.00	3.40	20.00
4	2	#NULL!	#NULL!	1	1	1	2	1	1.00	0.00	3.80	6.67
4	2	#NULL!	#NULL!	1	1	1	2	1	2.00	16.67	3.60	13.33
4	2	#NULL!	#NULL!	1	1	1	2	1	1.50	8.33	3.80	6.67
4	3	1	#NULL!	1	1	1	2	1	1.00	0.00	3.40	20.00
3	2	1	#NULL!	1	1	1	2	1	3.00	33.33	3.00	33.33
4	3	#NULL!	#NULL!	2	1	1	2	1	2.00	16.67	2.80	40.00
3	2	2	3	1	1	1	2	1	2.00	16.67	2.80	40.00

RF2_RS_1	RF2_1	EF_RS_1	EF_1	CF_RS_1	CF_1	SF_RS_1	SF_1	FA_RS_1	FA_1	NV_RS_1	NV_1	PA_RS_1
3.00	33.33	4.00	0.00	3.00	33.33	3.00	33.33	3.33	77.78	3.00	66.67	4.00
3.00	33.33	3.75	8.33	3.00	33.33	2.50	50.00	2.00	33.33	2.50	50.00	3.00
2.50	50.00	3.00	33.33	2.50	50.00	3.00	33.33	2.67	55.56	2.00	33.33	3.00
2.50	50.00	2.00	66.67	3.00	33.33	3.00	33.33	2.67	55.56	2.50	50.00	3.00
4.00	0.00	4.00	0.00	4.00	0.00	4.00	0.00	4.00	100.00	3.00	66.67	4.00
2.00	66.67	3.00	33.33	2.50	50.00	3.00	33.33	2.67	55.56	2.00	33.33	3.00
2.00	66.67	3.50	16.67	3.00	33.33	3.50	16.67	3.00	66.67	1.50	16.67	3.00
3.00	33.33	3.00	33.33	3.00	33.33	3.00	33.33	3.33	77.78	2.50	50.00	4.00
3.00	33.33	3.00	33.33	3.50	16.67	3.50	16.67	3.00	66.67	3.00	66.67	4.00
4.00	0.00	3.00	33.33	3.00	33.33	4.00	0.00	3.67	88.89	3.00	66.67	4.00
4.00	0.00	4.00	0.00	4.00	0.00	4.00	0.00	3.33	77.78	3.00	66.67	4.00
3.50	16.67	4.00	0.00	3.00	33.33	4.00	0.00	3.67	88.89	4.00	100.00	4.00
4.00	0.00	3.00	33.33	3.00	33.33	4.00	0.00	4.00	100.00	2.50	50.00	4.00
4.00	0.00	3.75	8.33	3.00	33.33	3.50	16.67	3.33	77.78	3.50	83.33	4.00
2.50	50.00	3.00	33.33	3.50	16.67	3.00	33.33	3.67	88.89	3.50	83.33	4.00
3.00	33.33	4.00	0.00	3.50	16.67	3.50	16.67	2.67	55.56	3.00	66.67	4.00
2.50	50.00	3.00	33.33	3.50	16.67	3.00	33.33	3.67	88.89	3.00	66.67	4.00

PA_1	DY_RS_1	DY_1	SL_RS_1	SL_1	AP_RS_1	AP_1	CO_RS_1	CO_1	DI_RS_1	DI_1	FI_RS_1	FI_1	RS_HNPA_1	HNPA_1	RS_HNSW_1	HNSW_1	RS_HNSE_1	HNSE_1	RS_HNSP_1
100.00	1.00	0.00	3.00	66.67	2.00	33.33	1.00	0.00	2.00	33.33	4.00	100.00	3.75	91.67	3.00	66.67	2.50	50.00	3.00
66.67	1.00	0.00	3.00	66.67	3.00	66.67	3.00	66.67	1.00	0.00	2.00	33.33	3.50	83.33	2.75	58.33	3.00	66.67	3.00
66.67	1.00	0.00	2.00	33.33	2.00	33.33	1.00	0.00	1.00	0.00	4.00	100.00	2.75	58.33	2.25	41.67	2.00	33.33	1.33
66.67	1.00	0.00	2.00	33.33	2.00	33.33	1.00	0.00	1.00	0.00	2.00	33.33	2.75	58.33	2.50	50.00	2.00	33.33	2.00
100.00	1.00	0.00	4.00	100.00	4.00	100.00	1.00	0.00	1.00	0.00	4.00	100.00	4.00	100.00	3.25	75.00	3.50	83.33	3.00
66.67	1.00	0.00	2.00	33.33	2.00	33.33	1.00	0.00	1.00	0.00	4.00	100.00	3.00	66.67	2.00	33.33	2.00	33.33	2.67
66.67	1.00	0.00	3.00	66.67	4.00	100.00	1.00	0.00	1.00	0.00	4.00	100.00	3.75	91.67	2.75	58.33	3.00	66.67	2.00
100.00	1.00	0.00	3.00	66.67	4.00	100.00	2.00	33.33	1.00	0.00	4.00	100.00	3.75	91.67	2.75	58.33	3.00	66.67	2.33
100.00	1.00	0.00	2.00	33.33	3.00	66.67	1.00	0.00	1.00	0.00	2.00	33.33	3.75	91.67	3.00	66.67	3.00	66.67	2.67
100.00	1.00	0.00	4.00	100.00	2.00	33.33	1.00	0.00	1.00	0.00	4.00	100.00	4.00	100.00	3.50	83.33	3.00	66.67	3.33
100.00	2.00	33.33	4.00	100.00	4.00	100.00	1.00	0.00	1.00	0.00	2.00	33.33	4.00	100.00	3.50	83.33	4.00	100.00	3.67
100.00	1.00	0.00	2.00	33.33	2.00	33.33	3.00	66.67	1.00	0.00	2.00	33.33	3.25	75.00	2.75	58.33	3.50	83.33	3.33
100.00	1.00	0.00	2.00	33.33	3.00	66.67	3.00	66.67	1.00	0.00	4.00	100.00	3.75	91.67	3.25	75.00	3.50	83.33	3.00
100.00	1.00	0.00	3.00	66.67	4.00	100.00	1.00	0.00	1.00	0.00	4.00	100.00	4.00	100.00	3.00	66.67	4.00	100.00	3.67
100.00	1.00	0.00	2.00	33.33	4.00	100.00	2.00	33.33	1.00	0.00	4.00	100.00	3.25	75.00	3.25	75.00	3.00	66.67	2.00
100.00	1.00	0.00	3.00	66.67	3.00	66.67	1.00	0.00	1.00	0.00	3.00	66.67	3.50	83.33	3.00	66.67	3.00	66.67	3.33
100.00	1.00	0.00	2.00	33.33	3.00	66.67	2.00	33.33	1.00	0.00	4.00	100.00	3.00	66.67	3.25	75.00	3.00	66.67	3.00

HNSP_1	RS_HNSO_1	HNSO_1	RS_HNSC_1	HNSC_1	RS_HNSX_1	HNSX_1	RS_HNTE_1	HNTE_1	RS_HNOM_1	HNOM_1	RS_HNDR_1	HNDR_1	RS_HNSS_1	HNSS_1	RS_HNCO_1	HNCO_1
66.67	2.75	58.33	3.20	73.33	0.00	-33.33	3.00	66.67	4.00	100.00	1.00	0.00	4.00	100.00	3.00	66.67
66.67	2.75	58.33	3.40	80.00	0.00	-33.33	2.00	33.33	3.00	66.67	1.00	0.00	3.00	66.67	3.00	66.67
11.11	2.75	58.33	2.60	53.33	0.50	-16.67	2.00	33.33	3.00	66.67	2.00	33.33	3.00	66.67	2.00	33.33
33.33	1.75	25.00	3.00	66.67	0.00	-33.33	2.00	33.33	3.00	66.67	2.00	33.33	3.00	66.67	3.00	66.67
66.67	3.50	83.33	3.20	73.33	0.00	-33.33	4.00	100.00	4.00	100.00	2.00	33.33	4.00	100.00	3.00	66.67
55.56	2.00	33.33	2.40	46.67	0.50	-16.67	2.00	33.33	3.00	66.67	2.00	33.33	3.00	66.67	2.00	33.33
33.33	3.00	66.67	2.80	60.00	2.00	33.33	3.00	66.67	4.00	100.00	1.00	0.00	4.00	100.00	3.00	66.67
44.44	2.75	58.33	3.00	66.67	2.50	50.00	3.00	66.67	4.00	100.00	2.00	33.33	3.00	66.67	4.00	100.00
55.56	2.75	58.33	3.00	66.67	0.00	-33.33	2.00	33.33	3.00	66.67	1.00	0.00	3.00	66.67	3.00	66.67
77.78	3.25	75.00	3.20	73.33	0.00	-33.33	3.00	66.67	3.00	66.67	2.00	33.33	4.00	100.00	4.00	100.00
88.89	3.50	83.33	3.20	73.33	0.00	-33.33	4.00	100.00	3.00	66.67	3.00	66.67	4.00	100.00	3.00	66.67
77.78	2.50	50.00	2.80	60.00	0.00	-33.33	4.00	100.00	4.00	100.00	3.00	66.67	1.00	0.00	3.00	66.67
66.67	3.25	75.00	3.20	73.33	0.00	-33.33	4.00	100.00	4.00	100.00	3.00	66.67	3.00	66.67	4.00	100.00
88.89	3.50	83.33	3.60	86.67	0.50	-16.67	3.00	66.67	4.00	100.00	3.00	66.67	1.00	0.00	3.00	66.67
33.33	3.50	83.33	2.80	60.00	0.50	-16.67	3.00	66.67	4.00	100.00	2.00	33.33	3.00	66.67	3.00	66.67
77.78	3.00	66.67	3.20	73.33	0.00	-33.33	3.00	66.67	3.00	66.67	2.00	33.33	3.00	66.67	3.00	66.67
66.67	3.00	66.67	3.00	66.67	2.50	50.00	3.00	66.67	3.00	66.67	1.00	0.00	4.00	100.00	3.00	66.67

RS_HNFI_1	HNFI_1	RS_PK_1	PK_1	RS_NU_1	NU_1	RS_FE_1	FE_1	RS_WL_1	WL_1	RS_WG_1	WG_1	QU1_2	QU2_2	QU3_2	QU4_2	QU5_2	QU6_2	QU7_2	QU8_2	QU9_2	QU10_2
4.00	100.00	2.00	100.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	1.00	3.00	3.00	3.00	3.00	1.00	4.00	3.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	1.00	3.00	3.00	3.00	3.00	1.00	4.00	2.00
3.00	66.67	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	2.00	1.00	1.00	2.00	2.00	3.00	1.00	3.00	2.00
4.00	100.00	2.00	100.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	2.00	2.00	2.00	3.00	3.00	2.00	1.00	3.00	2.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	3.00	4.00	4.00	3.00	3.00	1.00	4.00	3.00
3.00	66.67	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	2.00	1.00	3.00	2.00	2.00	2.00	1.00	3.00	2.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	3.00	3.00	1.00	3.00	4.00	2.00	2.00	1.00	4.00	2.00
4.00	100.00	2.00	100.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	2.00	1.00	2.00	3.00	3.00	3.00	1.00	4.00	3.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	2.00	1.00	2.00	3.00	3.00	3.00	1.00	4.00	3.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	4.00	2.00	4.00	4.00	3.00	4.00	1.00	4.00	4.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	2.00	3.00	4.00	3.00	3.00	1.00	4.00	3.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	3.00	4.00	4.00	3.00	4.00	1.00	4.00	3.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	4.00	3.00	4.00	3.00	3.00	3.00	1.00	3.00	4.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	4.00	2.00	4.00	4.00	3.00	3.00	1.00	4.00	4.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	2.00	3.00	2.00	3.00	2.00	1.00	4.00	4.00
4.00	100.00	2.00	100.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	1.00	3.00	4.00	3.00	3.00	1.00	3.00	3.00
4.00	100.00	1.00	0.00	1.00	0.00	1.00	0.00	2.00	100.00	1.00	0.00	4.00	3.00	1.00	3.00	4.00	2.00	3.00	1.00	4.00	3.00

QU11_2	QU12_2	QU13_2	QU14_2	QU15_2	QU16_2	QU17_2	QU18_2	QU19_2	QU20_2	QU21_2	QU22_2	QU23_2	QU24_2	QU25_2	QU26_2	QU27_2	QU28_2	QU29_2	QU30_2	QU31_2
3.00	4.00	2.00	3.00	2.00	4.00	1.00	3.00	3.00	3.00	4.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	5.00	4.00	4.00
4.00	4.00	4.00	4.00	2.00	3.00	1.00	2.00	4.00	4.00	3.00	3.00	1.00	3.00	3.00	4.00	2.00	3.00	3.00	3.00	3.00
2.00	3.00	3.00	3.00	2.00	3.00	1.00	3.00	3.00	2.00	3.00	3.00	1.00	1.00	2.00	3.00	3.00	4.00	6.00	5.00	4.00
2.00	3.00	3.00	4.00	3.00	3.00	1.00	3.00	3.00	3.00	2.00	2.00	2.00	2.00	3.00	2.00	2.00	4.00	4.00	4.00	4.00
3.00	4.00	3.00	3.00	2.00	4.00	1.00	4.00	4.00	4.00	3.00	3.00	3.00	3.00	3.00	4.00	3.00	4.00	1.00	1.00	4.00
2.00	3.00	2.00	3.00	2.00	2.00	1.00	3.00	3.00	2.00	3.00	3.00	1.00	1.00	3.00	3.00	3.00	4.00	5.00	5.00	3.00
4.00	3.00	4.00	4.00	2.00	3.00	1.00	4.00	4.00	3.00	3.00	4.00	4.00	2.00	3.00	3.00	2.00	3.00	5.00	4.00	4.00
3.00	4.00	4.00	3.00	2.00	4.00	1.00	3.00	3.00	3.00	4.00	4.00	2.00	2.00	3.00	3.00	3.00	4.00	4.00	4.00	4.00
4.00	4.00	4.00	4.00	2.00	2.00	1.00	3.00	2.00	3.00	3.00	3.00	1.00	3.00	2.00	3.00	3.00	3.00	4.00	4.00	4.00
3.00	4.00	2.00	4.00	3.00	4.00	1.00	4.00	4.00	3.00	4.00	3.00	2.00	3.00	3.00	3.00	3.00	3.00	1.00	1.00	3.00
3.00	4.00	3.00	3.00	3.00	4.00	1.00	4.00	4.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	4.00	3.00	2.00	2.00	3.00
2.00	4.00	2.00	3.00	3.00	4.00	1.00	4.00	4.00	4.00	3.00	4.00	2.00	2.00	2.00	3.00	4.00	4.00	2.00	2.00	4.00
2.00	3.00	3.00	3.00	2.00	4.00	1.00	4.00	4.00	4.00	4.00	4.00	3.00	3.00	2.00	4.00	3.00	2.00	2.00	2.00	4.00
3.00	4.00	3.00	4.00	3.00	4.00	1.00	4.00	4.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	3.00	2.00	2.00	3.00
2.00	4.00	4.00	3.00	2.00	3.00	1.00	3.00	3.00	3.00	4.00	4.00	3.00	1.00	2.00	3.00	3.00	4.00	4.00	3.00	4.00
3.00	4.00	4.00	4.00	3.00	1.00	3.00	2.00	3.00	3.00	3.00	3.00	1.00	2.00	2.00	4.00	3.00	3.00	5.00	4.00	3.00
2.00	4.00	4.00	4.00	3.00	2.00	1.00	4.00	3.00	3.00	4.00	3.00	1.00	2.00	2.00	3.00	3.00	4.00	3.00	3.00	3.00

QU32_2	QU33_2	QU34_2	QU35_2	QU36_2	QU37_2	QU38_2	QU39_2	QU40_2	QU41_2	QU42_2	QU43_2	QU44_2	QU45_2	QU46_2	QU47_2	QU48_2	QU49_2
3.00	3.00	3.00	3.00	3.00	4.00	3.00	3.00	2.00	3.00	2.00	2.00	4.00	2.00	3.00	3.00	4.00	2.00
2.00	3.00	4.00	4.00	4.00	4.00	3.00	2.00	2.00	3.00	3.00	1.00	3.00	2.00	1.00	2.00	3.00	4.00
2.00	3.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	3.00	3.00	1.00	3.00	2.00	2.00	3.00	3.00	4.00
2.00	2.00	3.00	2.00	2.00	3.00	1.00	2.00	2.00	3.00	3.00	1.00	2.00	3.00	2.00	2.00	3.00	3.00
4.00	3.00	3.00	2.00	3.00	3.00	2.00	2.00	2.00	2.00	4.00	3.00	4.00	3.00	3.00	3.00	3.00	4.00
2.00	3.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	3.00	3.00	1.00	2.00	2.00	2.00	2.00	3.00	4.00
2.00	3.00	4.00	1.00	2.00	2.00	1.00	3.00	2.00	3.00	3.00	3.00	4.00	2.00	1.00	3.00	3.00	3.00
2.00	2.00	3.00	1.00	2.00	3.00	1.00	3.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	4.00	3.00
3.00	3.00	3.00	3.00	3.00	4.00	2.00	2.00	2.00	4.00	3.00	3.00	3.00	3.00	2.00	2.00	4.00	4.00
4.00	4.00	3.00	1.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	2.00	3.00	3.00	3.00	2.00	3.00	4.00
3.00	3.00	3.00	3.00	3.00	4.00	2.00	3.00	2.00	3.00	3.00	3.00	3.00	3.00	3.00	2.00	2.00	2.00
4.00	3.00	2.00	3.00	3.00	4.00	1.00	3.00	2.00	3.00	1.00	3.00	4.00	2.00	2.00	3.00	4.00	3.00
3.00	3.00	1.00	1.00	2.00	3.00	1.00	3.00	1.00	3.00	3.00	4.00	3.00	2.00	3.00	3.00	4.00	3.00
3.00	3.00	3.00	4.00	4.00	4.00	3.00	2.00	2.00	3.00	1.00	3.00	3.00	3.00	3.00	3.00	3.00	4.00
3.00	3.00	3.00	2.00	3.00	4.00	2.00	4.00	3.00	3.00	2.00	1.00	4.00	2.00	1.00	3.00	3.00	2.00
3.00	1.00	3.00	3.00	3.00	4.00	1.00	2.00	3.00	3.00	3.00	1.00	3.00	2.00	1.00	2.00	3.00	4.00
2.00	3.00	3.00	2.00	3.00	3.00	2.00	3.00	3.00	3.00	2.00	3.00	3.00	2.00	1.00	3.00	3.00	4.00